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Dr. Jonathan C. Meakins

Dr. Jonathan C. Meakins, Emeritus Professor of Medicine, at McGill University, died at the Royal Victoria Hospital, Montreal, on October 12, 1959, after a short illness. He was seventy-seven years of age.

Jonathan Meakins was born in Hamilton, Ontario, in the year 1882, and was graduated in medicine at McGill University in 1904. After two years of internship and residency at the Royal Victoria Hospital, he spent a year with Rufus Cole in the Department of Bacteriology of Johns Hopkins, followed by two years in the Department of Pathology of the Presbyterian Hospital in New York, under Eugene Opie. He then returned to McGill and the Royal Victoria Hospital with the orthodox training expected at that time of a physician who had academic ambitions. He soon showed, however, that his outlook on medicine was far from orthodox. He had an inquiring mind and realized the importance of the physiological approach to medical problems. He was appointed Director of the Department of Experimental Medicine in McGill in 1912, but he soon resigned from this appointment and left for England to work with Thomas Lewis and Sir James MacKenzie. He returned to Montreal in July, 1914, in time to enroll in No. 3 General Hospital, which sailed for England in May, 1915. His real interest, however, was still in experimental medicine, and by the end of that year he had joined his old friend Sir Thomas Lewis to study "D.A.H." During the next three years he belonged to a team which investigated the physiological problems which arose from gas warfare and other hazards, a team which consisted of such leaders in science as Lewis, Dale, Haldane, Barcroft, and Cushny. By the end of World War I he was widely known as a sound physician who was also a brilliant investigator, and who had the drive, energy, and personality of the born leader. It did not surprise his friends when, soon after his return to Montreal, he was offered the Christison Chair of Therapeutics and Clinical Medicine at Edinburgh University. This he accepted at the age of 37.

In Edinburgh, he was one of the first to introduce scientific methods of research into the Royal Infirmary, and the laboratories which he planned remain a tribute to his energy and foresight. His gay, distinguished, and debonair manner also struck a new note in the professoriate. It would not be unusual for him to enjoy a jovial evening with the students and next morning deliver a fascinating lecture on the application of physiological principles to disease, and

then conduct a breezy round of the wards, attended in those congested postwar days by thirty or forty clerks. His life in Edinburgh was a full one, and yet he found the time to write the first book on respiratory function in disease, and was a member of Barcroft's expedition to the Andes, which made the first comprehensive study of the effects of high altitudes on man.

In 1924, he returned to Montreal as Professor of Medicine at McGill University and Physician-in-Chief at the Royal Victoria Hospital, where he made many changes in the old order. Naturally, he met with some opposition. This only served to strengthen his confidence in the merit of his plans and was treated as a challenge which he met with characteristic zest and vigor. He quickly established himself as one of the leaders in medicine on the North American continent. In 1929, he was elected the first president of the Royal College of Physicians and Surgeons of Canada, and five years later was elected President of the American College of Physicians and Surgeons. The next year he was President of the Canadian Medical Association.

At the outbreak of World War II he became Deputy Director of Medical Services in the Canadian Army, with the rank of Brigadier. In 1942, he was appointed Dean of the Faculty of Medicine at McGill University. He was editor of the *American Heart Journal*, and author of *The Practice of Medicine*, which went through six editions.

The honors which Dr. Meakins received in his lifetime include: C.B.E., D.Sc., LL.D. F.A.C.P., F.R.C.P. (Edin.), Hon. F.R.C.S. (Edin.), F.R.C.P. (Lond.), F.R.C.P. (C), F.R.S.C., F.R.S.E., and Emeritus Professor of Medicine at McGill University.

He is survived by his wife, the former Sarah Caldwell; one son, Dr. Jonathan F. Meakins, a senior attending-physician at the Royal Victoria Hospital; a daughter, Diana; and a sister, Florence Meakins, of Hamilton, Ontario. Also surviving are three grandchildren.

Dr. Meakins will be remembered by his colleagues for his magnetic and forceful personality and the prominent part he took in Canadian and North American medicine.

He will be remembered also by the loyal band of those he trained, for his friendly leadership, his integrity, and the stimulation of his quick and accurate mind.

But long after his friends and colleagues have followed him, he will be remembered as a pioneer in applying scientific methods to medicine. He will take his place in medical history as the first to make an organized effort to investigate the disturbances of function which occur in diseases of the lung, an effort which culminated in the publication in 1925, of his book, *Respiratory Function in Disease.*

His name will also be recorded in the annals of Edinburgh University and McGill University as the person who introduced an atmosphere of scientific inquiry and research into their teaching hospitals.

Ronald V. Christie, M.D.
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Editorial

The International Study of Coronary Heart Disease

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There are fashions in cardiology as well as in art or in women's dresses. In the early nineteen-forties, advances in electrocardiography, empirical and theoretical, centered around the problem of "coronary insufficiency," and it was believed that much could be gained by recognition of early clinical coronary heart disease, and the subsequent institution of prophylactic treatment, with a healthful regimen and vasodilating drugs.

Meanwhile, the cardiac catheter and the cardiac surgeon appeared on the stage: coronary heart disease was still useful for the practicing cardiologist's daily living, but blue babies, mitral stenoses, hypothermia, and extracorporeal circulation became, in turn, the really fashionable things. By now, the surgeons have succeeded even in interchanging the pulmonary and the systemic circulations (in patients with transposition), and this is probably close to the boundaries of the surgeons' territories. In the last few years—and because leading statesmen are publicly affected by it—coronary heart disease has again come into focus, with "atherosclerosis and the diet" being the new scientific fashion.

Against the background of an increasing number of deaths due to coronary heart disease, and, at the same time, the apparent and unexplained differences in frequency between various populations, the diagnostic problem of clinical coronary heart disease of the early nineteen-forties was transformed into an *epidemiological* challenge to scientists in the middle of the nineteen-fifties.

The study of international mortality statistics gave the impression that the frequency of coronary (or rather "arteriosclerotic") heart disease varied considerably, not only from one period to another *within the same* population (e.g., Scandinavia during the war years), but also *between* countries. It is possible that the latter variation can be explained, at least in part, on the basis of the populations in question having arrived at different parts of a common curve of development.

It was very soon apparent to those interested in these problems that one could not be too sure of the comparability of data from different national sources.

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The pioneering enterprises of Ancel Keys and Paul D. White in the campaign to collect primary data having a high degree of comparability should be recognized, not only by their many collaborators but also by cardiologists throughout the entire world. In the Joint Report of the Research and Social Committees of the International Society of Cardiology, agreed upon during the Third World Congress of Cardiology in Brussels in 1958, attention was drawn to the needs for further international scientific cooperation in world-wide campaigns against cardiovascular diseases. The standardization of methods, tests, and reporting of findings was stressed as a basic need, and this relates both to medical and personal history, physical examinations, electrocardiography, radiology, and the analysis of certain blood constituents. The assistance of the World Health Organization to that end was anticipated.

A considerable amount of substantial information has already been collected both by international research teams and by local studies in some countries. What we know today—and we know at least something, although there are differences of opinion as regards interpretation—is almost entirely due to the initiative of a limited number of research workers who have learned the hard rules of modern epidemiology. It has been said by Claude Bernard that laboratory experiments are also performed on a large scale by Nature, and that the one who asks the right questions will also read the right answers in the book of Nature. Many casual observations may be collected in this way, but experience has shown that often there are too many unverified and unverifiable variables in Nature to make conclusions valid. Also, in Nature most experiments must be carefully designed in advance, and then they will probably give the best results. Another thing is that some information *is* already historical; we must take it or leave it, and it is a completely unwarranted snobbism only to "leave it."

On the other hand, the present interest in the "epidemiological method" has stimulated the production from all corners of the world of a great many studies and papers on which much energy has been wasted because the data are neither obtained nor reported in categories that will fit into an international comparison. As long as this continues, we are losing time and important information. It is of the greatest importance, therefore, that the two international agencies that have the possibilities of joining together to integrate research efforts on cardiovascular diseases all over the world—The World Health Organization and the International Society of Cardiology—really do so. There is a painful difference between the substantial results collected by the aforementioned research teams and the voluminous reports and recommendations offered by the two international bodies. Why is that so? Everyone who has had the slightest contact with international collaboration in any field knows how much time and effort have to be spent on "procedures," formalities, and semantic difficulties. Furthermore, at least up to the present time, these organizations have had rather limited budgets. Thus, because of a pernicious central weakness, peripheral efforts remain insufficiently coordinated and may result in next to nothing.

In this connection it should be stated here that the World Health Organization *has* already done quite a lot in order to coordinate research efforts and preventive measures in cardiovascular diseases. The foolish thing is that the World

Health Organization, being an organization of governments, and staffed chiefly by public health administrators—which is probably very well as long as the problem is malaria or malnutrition—has insufficient connection with universities, medical schools, research institutes, scientific societies, and scientific journals. Consequently, WHO information does not "get through." There is a shocking lack of knowledge in the scientific world of WHO endeavors in various fields. Basically, the International Statistical Classification of Diseases and Causes of Death, compiled and published by WHO, is our fundamental instrument in comparing death statistics (also as regards coronary heart disease) from various countries. No comparison of raw data will be any better than is the material provided by the various member countries of the World Health Organization. Unfortunately, present nomenclature and codification of these diseases is disturbingly inadequate. This is a source of annoyance and disquietude to those who work in the field, and such feelings are shared by officers within the World Health Organization who eagerly look forward to a revision of the Classification.

Among other manifestations of WHO interest in coordination of research in coronary heart disease may be mentioned WHO Technical Reports* No. 117 (1957), by the study groups on atherosclerosis and ischemic heart disease; No. 143 (1958), on "classification of atherosclerotic lesions," which gives detailed recommendations for comparative pathologic-anatomic studies on atherosclerosis; and No. 168 (1959), which concerns "hypertension and coronary heart disease: classification and criteria for epidemiological studies." In addition to these general reports and recommendations the Regional WHO Office for Europe has convened groups of research workers for special coordination purposes.

Against this background, some specific headaches in international epidemiological work may be commented upon.

1. *What does "coronary heart disease" mean in an "epidemiological" sense as compared to "clinical coronary heart disease"?* Many people who see their doctors because of symptoms—say, of angina pectoris—do not show any objective signs of disease, not even on electrocardiograms. On the other hand, when a population, is screened, many people show electrocardiograms indicating myocardial damage, presumably "coronary" in origin, without giving a history or having symptoms. Finally, it is well known that a considerable degree of coronary atherosclerosis may be found at autopsy in people who have had neither symptoms nor signs of coronary heart disease.

Thus, coronary heart disease resembles an iceberg, a part of which may be observed, but the major part of which may, perhaps, be unknown as to extent or even presence. When we record "coronary heart disease" in *morbidity* surveys or *mortality* statistics, we may record, at best, a uniformly defined *fraction* of the total coronary heart disease population. Comparison of uniformly defined *fractions* may have a value as indicators of the *total*, but this is not necessarily so. However, as yet, probably no better assumption can be made. The most

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*All World Health Organization Technical Reports may be obtained by payment in local currency, directly or through a bookseller, from national agencies. From Columbia University Press, 2960 Broadway, New York 27, N. Y., U.S.A.; or WHO Distribution and Sales Unit, Palais des Nations, Geneva, Switzerland.

easily defined fraction, in our opinion, is the clinically established myocardial infarct. An infarct, however, is an acute event in a progressive chronic disease. We know very little about the actual provoking factors, the "triggers," and it may well be that some cultural settings provide many more "triggers" than others. Still, clinically established infarcts appear to be a more reliable indicator than anything else. The problems are that there is a selection factor, varying from place to place and from time to time, as regards the fraction of infarct patients that are brought to hospital, or otherwise become diagnosed as such. Hospital figures therefore, may be used only when the selection bias can be reasonably well checked, and when the autopsy control is extensive.

The alternative to the use of infarcts as indicators—and in contrast to infarcts they are useful only in *mortality* studies—is the use of "sudden deaths." WHO Report 168 has recently stated that this cannot be considered justified at present, because the term "sudden death" is taken to mean so many different things. If it really means *instantaneous* death, it might be used as an index of something—probably of ventricular fibrillation or asystole, consequent to some underlying coronary or myocardial damage—but not necessarily thrombosis or occlusion. What relationship such happenings really have to other, and probably more common, manifestations of coronary heart disease we do not know. Probably the most reliable index we have at present is the frequency of well-defined *myocardial scars*, traced *at autopsy*. More work should be done in this field, in which information seems to be the most objectively assessable.

2. *Are we justified in separating, for convenience, one group of younger, more "typical" patients from another group of older patients with less "typical" symptons; and are we justified to concentrate on the first group and disregard the other one?* My team of researchers is very doubtful about the validity of that tendency, although we can see few ways around the difficulty which affects the study of the older age-groups, viz., the lack of specificity of diagnosis on the death certificate in such cases. But when studies of people with myocardial infarction who are below the age of 40 (White and Gertler), or 55 (Forssman and Lindegård), or even 59 (Keys) or 64 (British statistics) are presented, one might point to two observations in our material: (a) infarct patients under 40 years of age probably derive from a different "population" (as regards cholesterol values) than other infarct patients (Biörck and associates, Oliver and Boyd), and (b) the mean age at *first* infarction in our material of 1,612 infarct patients is now 62 years for men and 68 for women, and these mean ages have increased by about 5 years during the twenty-year period from 1935 through 1954. This means that the younger the fraction studied, the greater the impact of "abnormal" populations within the group. But it also means that if for some reason—and Hardin Jones has presented interesting evidence to that end—"biological" age and "chronological" age do not coincide, then cutting off the sample at a certain age—which in most materials, as judged by our figures, would leave half or more than half of the primary infarcts out—may result in "cuts" at different levels in the biological age-groups series and result in a false comparison. The higher one goes age-groupwise, probably the less is this particular risk. Therefore, every effort should be made by those who work with limited age-groups to compile

and compare simultaneously material from total—age group—materials, at least in the range from 40, or 30, years of age and upward.

3. *What are the reasons for differences in reported prevalence of coronary heart disease, and what are the pitfalls in the interpretation of international and national statistics?* Some of the reasons for reported differences are obviously *technical* in nature. Not all countries (not even all the larger ones) have adopted the International Classification of the World Health Organization, and even those who have done so, apparently do not always technically treat the data in the same way. Unfortunately, the WHO Classification as regards coronary heart disease (B 26, 420-422) is anything but useful for its alleged purpose, and is apt to create confusion* This fact is recognized even in WHO quarters, whence come recommendations for its revision (WHO Technical Report No. 161). To these formidable technical difficulties should be added the following reasons for differences, which are in a sense "real," but which have little to do with the cardiac lesion as such: namely, (a) semantic differences, and (b) lack of accuracy of diagnosis.

a. *Semantic differences:* These are due to varying concepts of disease mechanisms and disease patterns, also expressed in untranslatable differences in use of linguistic terms. In this regard, an interesting project was recently discussed within the European office of WHO; viz., the circulation of a number of histories of "coronary" patients, along with examination findings and possibly some laboratory data, to a number of physicians in various countries, in order to see how they would diagnose the case and what cause of death they would give. The results of such a project would give a picture of the extent of the semantic differences.

b. *Lack of accuracy in diagnosis:* Paton has recently revealed a shocking lack of accuracy in the diagnosis of myocardial infarction in a hospital material, as revealed by autopsy studies. "Observer errors," of an annoying degree, in the interpretation of electrocardiograms were likewise reported in a comparative study by Thomas and associates. Swedish studies by Malmström, Malmros Biörck and associates indicate that a more reasonable degree of accuracy can be achieved, at least in selected materials. However, much more work is required on the national level in order to measure—and thereby reduce—the lack of diagnostic accuracy. This is more a task for the National Societies of Cardiology than for the World Health Organization or other international organizations.

Some of the above-mentioned difficulties can probably be defined and, at least partly, overcome, and all efforts should be directed to that purpose. Only then will it be possible to state the size of the problem of the *residual* differences, which may be the *real* differences in prevalence, whether this relates to morbidity or mortality.

4. *What kind of ad hoc prevalence studies can be recommended in order to ensure international comparability?* It is our belief that the performance of prevalence studies, with international comparability in mind, should be planned by some international clearing-body and supervised locally—with the enlistment of a

*For example, myocardial infarction is recorded as 420, cardiac rupture as 422.

qualified local staff—by members of an international epidemiological team. At present, considerable *international* experience is being accumulated, particularly by members of Keys' group, whereas *local* experience is prevailing in several places. It is logical that a fusion of WHO administrative machinery and existing scientific experience be achieved, and the International Society of Cardiology could and should assist here.

This, however, does not relieve the substantial difficulty that lies in the choice of comparable populations. Several possibilities have been proposed: (a) *A sample of the whole population:* Sampling of a whole population has never been done. It meets with great difficulties, and is probably expensive as regards establishing centers of examination, but it could be tried in small, densely populated countries. Statistically it should be the ideal solution. (b) *A sample of a community:* The community to be sampled should as closely as possible resemble the whole population, and, by inference, could "represent" the whole population. This pertains particularly to age and sex composition, occupations, and mortality rates. A variant of this would be the use of samples from a *number* of smaller communities, which together might "represent" the whole population. This solution is probably somewhat more feasible from a practical point of view, but needs to be better defined. (c) *Total populations:* Study of a total population in certain age- and sex-groups from small communities, as preferred by Keys, could be carried out. In such instances one does not know the "local bias," and it will not be possible to generalize extensively from the findings. (d) *A sample of one or several occupational groups:* This type of study was originally done by Keys (Rotarians, clerks, firemen, heavy-workers) and by Morris. Provided suitable groups are selected (doctors, teachers, clergymen, policemen, railway-men, civil servants, etc.) and the principles of their selection defined, this might ensure a certain degree of comparability. However, there are certain pitfalls—apart from the primary selection of candidates for jobs and jobs for candidates—namely, the dropping out from the original "cohort," so that one may find oneself measuring the healthy residues rather than those afflicted with the disease.

Calculations on expected deaths from coronary heart disease in "active" age-groups show that the basic populations in prevalence studies have to be rather large (many thousands of persons) in order to give significant "dividends." The longer the duration of the follow-up, the greater the "dividend," and the smaller can be the size of the original population. Inasmuch as *prospective* studies, such as those in Framingham, Mass., and Albany, N. Y., U.S.A., are much more valuable than single prevalence surveys, it is to be strongly recommended that future prevalence studies be performed in a way that permits follow-up studies. Such can be done with studies both in local areas (communities) and in occupational groups. The prerequisites in both cases are reasonably stable "populations" and a permanent examination "machinery."

From this survey it is clear that a really active international clearing-house must be established, with facilities, finances, and authority to assist in the planning of further, sensible international projects in this field. At the Twelfth Assembly of the World Health Organization this year a research budget was established

within the organization. It is intended that research should be directed, *inter alia*, to cardiovascular diseases. A special officer for cardiovascular diseases, Dr. Z. Fejfar, a well-known cardiological physiologist, has been appointed to give advice and to supervise the administration of such research. It, therefore, seems reasonable to try to establish the long-desired and long-awaited international coordination center for cardiovascular research in general, and research on coronary heart disease in particular, in close connection with the World Health Organization. At this moment it seems also as though the World Health Organization is ready to abandon its red-tape, "for governments only," bureaucratic attitude toward the men who are practicing medicine in the field, and to be more willing than before to invite initiative and suggestions from the active "outsiders." May I therefore close this editorial with a final recommendation to the cardiologists of the world to write to "their congressmen" also in matters of world health—the World Health Organization, its headquarters or regional offices, or their own government representatives on its respective executive boards.

Clinical Communications

Cyanotic Spells and Loss of Consciousness Induced by Cardiac Catheterization in Patients With Fallot's Tetralogy

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Several publications dealing with the clinical and hemodynamic findings in Fallot's tetralogy have appeared in recent years.[1-3] However, we have been able to trace only two previous publications detailing the mechanism of production of cyanotic spells and loss of consciousness during cardiac catheterization.[2,4]

This paper reports our experience with 5 patients with Fallot's tetralogy who, following cardiac catheterization, showed either an increase in the severity of a cyanosis which was already present, or the first appearance of cyanosis. Two of the patients became unconscious. We discuss the clinical picture, pathogenesis, and treatment of these spells, and the cyanosis and attacks of unconsciousness occurring spontaneously in Fallot's tetrad. Emphasis is placed on the hazards of cardiac catheterization in both the "acyanotic" and cyanotic varieties of this syndrome.

PROCEDURE OF CARDIAC CATHETERIZATION

Premedication usually comprised appropriate intramuscular doses of meperidine hydrochloride, prochlorperazine maleate (or chlorpromazine hydrochloride), and promethazine hydrochloride, administered about 1½ hours prior to the procedure. If necessary, the patients were given general anesthesia in addition, consisting of small doses of methitural sodium—5-(1-methylbutyl)-5-[2-(methylthio)-ethyl]-2-thiobarbiturate—or thiopentone sodium. Oxygen was not administered routinely. The anesthetist attempted to maintain a steady state without respiratory depression throughout the procedure. Catheterization was performed in the usual manner, using a brachial vein at the elbow or near the axilla. The pulmonary artery was entered in each case. The relevant results and clinical findings in the 5 patients are summarized in Table I. Two previously acyanotic patients developed clinical cyanosis, with some decrease in intensity of the systolic murmur. Of 2 patients who were initially cyanosed, one reacted with an increase in the cyanosis and a decrease in pulmonary arterial pressure (Fig. 1), and the other with the development of unconsciousness at the end of the examination.

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TABLE I

CASE	CLINICAL CYANOSIS		PULMONARY EJECTION MURMUR		PULMONARY ARTERIAL PRESSURE (MM. Hg)			DURATION OF CYANOSIS		DURATION OF UNCONSCIOUSNESS	THERAPY	EFFECT	SEQUELAE
	AT REST	ON EFFORT	AT REST	DURING CATHETERIZATION	AT REST	CYANOTIC SPELL	SYNCOPAL SPELL	A	B				
1.	−	+	Loud	Softer	—	34/20	—	15 min.	—	—	Nil	—	Nil
2.	−	+	Loud	Softer	—	42/20	—	20 min.	—	—	Nil	—	Nil
3.	−	+	Loud	Absent	30/10	—	25/5	4 hr.	—	2½ hr.	Intravenous procaine	Excellent but transient	Nil
											Morphine	Good and sustained	
											100% oxygen	Nil	
4.	+	++	Loud	Softer	22/6	10/5	—	—	6 hr.	—	100% oxygen	Nil	Nil
5.	++	+++	Loud	Absent	25/10	—	—	—	8 hr.	96 hr.	Intramuscular morphine	Nil	
											Intravenous procaine	Nil	
											Intravenous aminophylline	Nil	
											Intravenous papaverine	Nil	Nil
											100% oxygen	Nil	
											Taussig-Blalock anastomosis	Maintained life until obstruction passed	

+ = Mild. ++ = Moderate. +++ = Marked.
A: Patient not previously cyanosed. B: Increase in cyanosis in patients previously cyanosed.

CLINICAL DESCRIPTION OF THE ATTACK

The features of the cyanotic and unconscious spells are summarized in Table II.

Induced Attacks.—In cases of induced attacks the cyanosis and/or loss of consciousness may be protracted. In two patients (Cases 1 and 2) cyanosis persisted for only 10 to 15 minutes. However, in a third case (Case 4) the patient remained cyanosed, with marked tachycardia and diminution of the systolic murmur for 6 hours after the catheterization had been completed. She did not lose consciousness, her pupils remained normal, and the superficial tendon reflexes were unchanged. The fourth patient (Case 3) was recently reported in detail.[5] She remained deeply unconscious, with the full clinical picture as described in Table II. After 2½ hours the spell was temporarily relieved by intravenous procaine. Eventually the attack was ended by intramuscular morphine sulfate.

TABLE II

SYMPTOMS AND SIGNS	NORMAL STATE	CYANOTIC SPELL	UNCONSCIOUS SPELL
Cyanosis	Nil to severe	Moderate to severe	Always severe
Hyperpnea	Nil	Moderate	Marked
Respiratory Rate	Less than 30 per minute	Over 40 per minute	Over 60 per minute
Sweating	Nil	Nil	Nil
Pulse Rate	95 to 115 per minute	145 to 160 per minute	165 to 180 per minute
Systemic Blood Pressure	Normal	Normal	Normal
Jugular Venous Pressure	Slightly elevated	Slightly elevated	Slightly elevated
Pulmonary Ejection Murmur	Loud and fairly long	Soft and short	Absent
Pulmonary Arterial Pressure	Normal or slightly reduced	Normal or reduced	Normal or markedly reduced
Arterial Oxygen Saturation	80 to 92 per cent	50 to 85 per cent	10 to 50 per cent
Tendon Reflexes	Normal	Normal to increased	Increased + clonus
Plantar Response	Flexor	Flexor	Extensor
Size of Pupils	Normal	Normal to small	Small to pin-point

The fifth case was clinically the most severe. He had had frequent syncopal attacks prior to catheterization. At the end of the procedure, while the skin incision was being sutured, his cyanosis increased and be became deeply unconscious, with small pupils. His systolic murmur disappeared (Fig. 2). The increased cyanosis and unconsciousness persisted, and after 8 hours an emergency Taussig-Blalock anastomosis was performed. With the administration of succinylcholine chloride and tracheal intubation at the commencement of the general anesthetic, his cyanosis disappeared, and the systolic murmur became pronounced for the first time. After the operation his color improved but the systolic murmur disappeared once more. He remained unconscious for 96 hours postoperatively, with hyperreflexia, ankle and knee clonus, and extensor plantar responses. The pupils remained small but not pin-point. As he emerged from his coma, he could not see, but his vision slowly improved and he began to talk. The loud systolic murmur finally returned after 7 days (Fig. 2). He lost his knee and ankle clonus but the reflexes remained hyperactive.

Spontaneous Attacks.—Cyanotic spells and loss of consciousness often occur *spontaneously* in cases of Fallot's tetralogy. Occasionally, patients with tricuspid atresia or with transposition of the great vessels with pulmonic stenosis suffer from these attacks. These spells frequently appear in the morning after a good night's rest. They may be induced by crying and pain. Rapid deep breathing (hyperpnea), tachycardia, irritability, restlessness, and increasing cyanosis soon appear. The child often assumes the knee-chest position and lies on his abdomen. The condition persists for seconds to minutes and may then pass. In other instances it persists, cyanosis becomes intense, and the patient becomes unconscious, with or without convulsions. In such cases an attack may be fatal, but usually consciousness is regained within a few minutes. During the attack the pupils

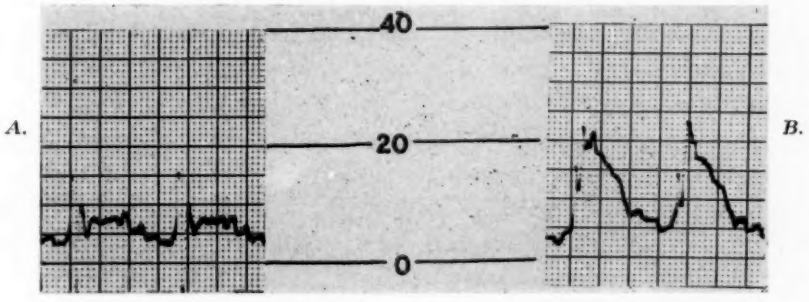

Fig. 1.—*A*, Pulmonary arterial pressure during cyanotic spell. *B*, Pulmonary arterial pressure before cyanotic spell.

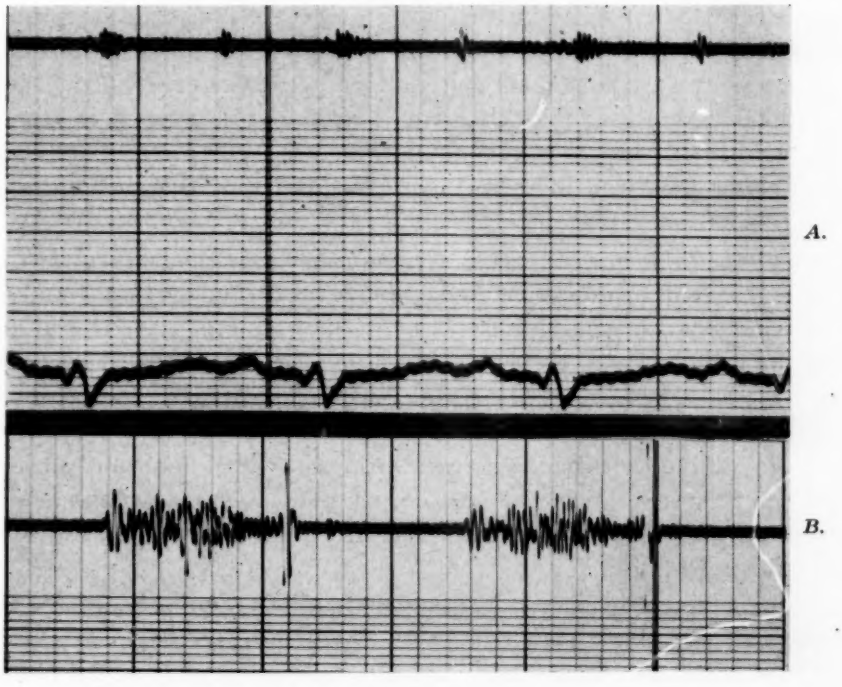

Fig. 2.—Phonocardiogram showing minimal systolic murmur during a spell of unconsciousness (*A*), with a loud, long, ejection systolic murmur after relief of the spell (*B*). Pulmonary area log. 5.

are equal and extremely small. The superficial tendon reflexes are markedly increased, with knee and ankle clonus in the deeply comatose patients. The plantar responses are extensor. The heart rate is very rapid (150 to 180 per minute), and the blood pressure is normal. In mild cases the systolic murmur is shortened and decreased in intensity, whereas in severe cases it may be completely absent. Sweating is not a feature.

PATHOGENESIS

The patients in this series have been severely ill, and the hemodynamic findings have been observed during routine diagnostic studies. Believing that any prolongation of the procedure could be hazardous, we have not attempted to measure flow during cyanotic or syncopal spells. The lack of flow measurement has precluded a definite determination of the pathogenesis of the spells. However, we have attempted, on the basis of pressure and auscultatory changes, to formulate an hypothesis explaining the attacks.

The cyanosis may be due to an increased right-to-left shunt at the ventricular level, although it could be increased by an over-all diminution in cardiac output. Three mechanisms could be responsible for an increased right-to-left shunt: (1) a decrease in systemic resistance, (2) an increased pulmonary arterial resistance, or (3) an infundibular obstruction.

1. *Decrease in Systemic Resistance.*—In two of our patients the parents noted a deterioration in effort tolerance together with an increase in cyanosis in hot weather. Presumably, the peripheral vasodilatation induced by the hot atmosphere decreases the systemic resistance and therefore permits an increase in the right-to-left shunt. However, in the attacks which we are describing the systemic blood pressure has remained uniformly unaltered (Fig. 3), and it is thought unlikely, therefore, that decreased systemic resistance is responsible. Moreover, we have found that the inhalation of amyl nitrite in patients with Fallot's tetralogy results in increased cyanosis, and that this only occurs when the systemic blood pressure falls.[6]

2. *Increased Pulmonary Arterial Resistance.*—This mechanism is excluded in Case 4 (increased cyanosis in a previously cyanosed patient) and Case 3 (syncopal attack), because in these patients the pulmonary arterial pressure fell during the attacks. In Cases 1 and 2 the pulmonary arterial pressure was at, or just above, the upper limits of normal during the attacks. Significant left-to-right as well as right-to-left shunts were present. Because anoxia per se can cause an increase in pulmonary arterial resistance, this factor may be present as a sequela rather than a cause of the spell. Such an increase in pulmonary arterial resistance could mask a drop in pulmonary arterial pressure produced by diminished pulmonary flow.

That anoxia alone can cause a striking increase in pulmonary arterial pressure in patients with acyanotic Fallot's tetrad was demonstrated in a case not included in this series. In this patient, anoxia was due to pharyngeal obstruction induced by a falling back of the tongue. He had a normal pulmonary arterial pressure and systemic arterial oxygen saturation at rest, with a large left-to-

right shunt at the ventricular level. With the development of anoxia the pulmonary arterial pressure rose significantly (Fig. 4), but no clinical features of a cyanotic spell ensued.

3. *Infundibular Obstruction.*—Infundibular obstruction will result in an increase in the amount of blood shunted from the right ventricle to the aorta, by increasing the resistance to the flow of blood from the right ventricle to the pulmonary artery. The diminution in the systolic murmur, the drop in pulmonary

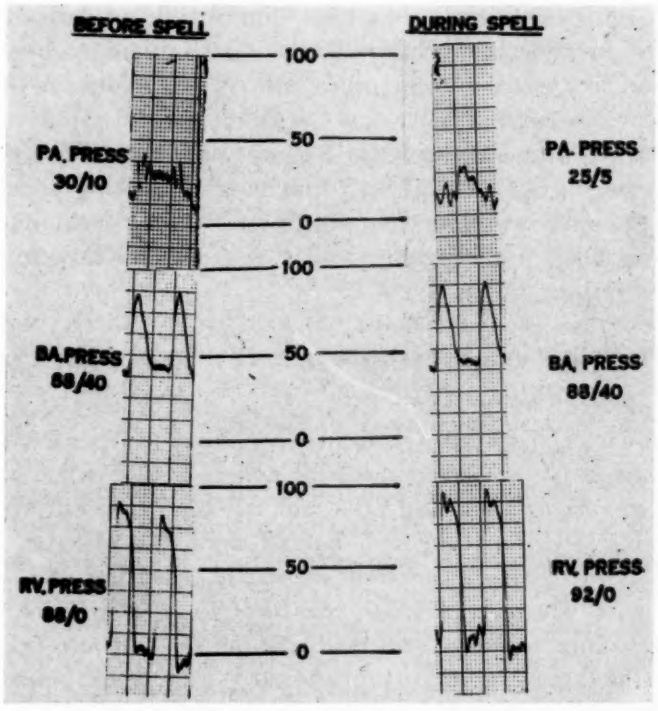

Fig. 3.—Pulmonary arterial, brachial arterial, and right ventricular pressures before and during a spell of unconsciousness.

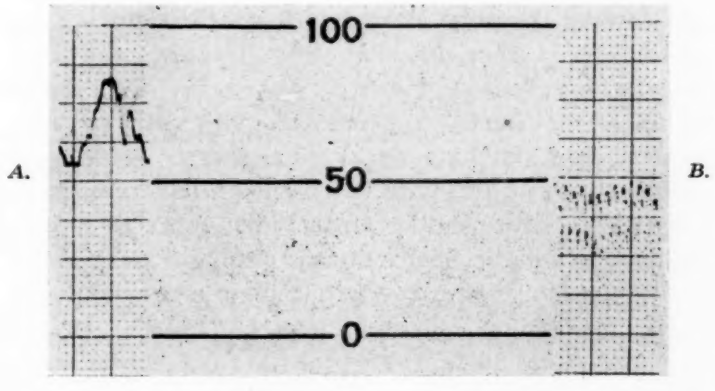

Fig. 4.—*A*, Pulmonary arterial pressure during anoxia. *B*, Pulmonary arterial pressure after relief of anoxia.

arterial pressure, and the maintained level of systemic blood pressure (Fig. 3) would be adequately explained. Tachycardia per se is not responsible for a diminution in the systolic murmur, because the murmur may vary from being barely audible to being very loud, without any alteration in the heart rate.[5] We believe, therefore, that this mechanism explains the induced attacks and probably some, if not all, of the spontaneous attacks, since the clinical features of the spontaneous attacks do not differ from those of the attacks induced by cardiac catheterization. In patients with severe pulmonary stenosis and intact ventricular septum, cyanotic attacks with diminution or disappearance of the systolic murmur do not occur. Infundibular obstruction may develop, but in these cases the right ventricular pressure can rise to maintain pulmonary flow at or near its previous level.

The *cause* of spontaneous spells in Fallot's tetralogy is unknown. The fact that they frequently occur after a restful night is interesting. Could there be an effect of the autonomic nervous system acting on the infundibulum of the right ventricle, causing it to become temporarily narrower? The effect of serotonin is also worthy of investigation.

DEGREE OF ANOXIA AND ITS RELATIONSHIP TO SYNCOPAL AND CYANOTIC SPELLS

Unlike Wood,[4] we have found that severe and prolonged unconsciousness may occur with arterial oxygen saturations of over 50 per cent. In the mild attack characterized by the appearance of cyanosis at cardiac catheterization, the arterial oxygen saturation may be about 82 to 85 per cent. We believe that the degree of arterial saturation will depend upon the severity of obstruction at the infundibular region of the right ventricle. Furthermore, it is suggested that those patients who are normally moderately to markedly cyanosed may require a decrease in arterial saturation to 20 per cent or less before losing consciousness. The acyanotic or mildly cyanosed patient may become unconscious at a much higher level of arterial oxygen saturation, namely, 50 per cent.

DANGERS OF CARDIAC CATHETERIZATION IN TETRALOGY OF FALLOT

In all of the patients with Fallot's tetralogy whom we have catheterized, the catheter has entered the pulmonary artery via the right ventricle. The mere presence of the catheter in the pulmonary artery increases the obstruction in the infundibular tract. However, evidence of persistent infundibular obstruction may be present for several hours after removal of the catheter. Even though the catheter had been in the pulmonary artery for as short a period as only 2 minutes in Case 4, an increase in cyanosis with diminished intensity of murmur persisted for 6 hours after the procedure had been concluded. Since we have become aware of the production of cyanotic spells during cardiac catheterization, we have observed some degree of infundibular obstruction in each case.

THERAPY

1. *Attacks Induced by Cardiac Catheterization.*—Wood noted some reduction in cyanosis with the administration of 100 per cent oxygen. He also demonstrated

the relief of infundibular spasm with the administration of cyclopropane anesthesia. The deepening of the level of anesthesia in our Case 3 abolished ankle and knee clonus and decreased the hyperpnea, but did not remove the increased infundibular obstruction, and the systolic murmur did not return. In this case, intravenous procaine was completely effective on two occasions, but the effect was only temporary. However, in Case 5, procaine given intravenously on three separate occasions was completely ineffective, as was intramuscular morphine. Intravenous papaverine hydrochloride, in doses of 15 and 30 mg., produced no change. Likewise, intravenous aminophylline, in doses of 60 and 90 mg., had no effect on his clinical condition. He remained deeply unconscious, and no systolic murmur was audible.

About 8 hours after the beginning of the spell, preparations were made for an emergency Taussig-Blalock anastomosis. During intubation, after the administration of succinylcholine chloride, the murmur returned; his color improved immediately but the state of consciousness was unchanged. After the left subclavian-pulmonary artery anastomosis had been completed, his cyanosis all but disappeared.

2. *Spontaneous Attacks.*—Most of the spontaneous spells pass without any medication. They usually persist for seconds to minutes. Morphine, by the oral, rectal, or parenteral route, has been recommended by Taussig.[7] In our experience of some 40 cases it has been of only limited value prophylactically and therapeutically. Intravenous aminophylline is ineffective. Oxygen therapy may reduce the cyanosis but has no curative action in an unconscious spell. The adoption of the knee-chest position—similar to squatting—may alleviate an attack. In view of its success in one case of an induced spell, intravenous procaine is worth a trial. The elevation of left ventricular pressure by vasopressor agents, e.g., mephentermine sulfate, could decrease the right-to-left shunt induced by infundibular obstruction, and thereby increase the volume of blood available for perfusion of the lungs. This form of therapy has to date not been tried.

SUMMARY AND CONCLUSIONS

1. Cardiac catheterization in acyanotic and cyanotic varieties of Fallot's tetralogy is not without danger. Cyanotic spells have been produced in 3 patients and syncopal attacks in 2.

2. The clinical findings in cyanotic and syncopal attacks are described. The diminution or disappearance of the systolic murmur, the maintenance of a normal blood pressure, the increase in or first appearance of cyanosis, and, in syncopal spells, the increased reflexes and extensor plantar responses, with pin-point pupils and loss of consciousness, are the main features.

3. The pathogenesis of the induced and spontaneous spells in Fallot's tetrad is discussed. Infundibular obstruction with consequent decreased pulmonary blood flow and increased right-to-left shunt through the ventricular septal defect is probably the most important factor in their production. The pulmonary arterial pressure may be normal or even mildly elevated in cyanotic spells produced in cases of acyanotic Fallot's tetralogy, but in syncopal attacks the pulmonary arterial pressure drops.

4. Therapy of the induced attack is discussed. Various drugs have been tried. In one patient, intravenous procaine hydrochloride had a significant though transient effect. In another it was completely ineffective. Intravenous papaverine hydrochloride and aminophylline were without effect in one patient. An emergency Taussig-Blalock anastomosis proved to be lifesaving in the same patient. Cyclopropane anesthesia and morphine sulfate have been recommended by others, and in one patient in this series, morphine was effective. However, there is as yet no known specific therapy for the attacks.

We are indebted to Dr. J. Meyer and Dr. W. F. Scott for their assistance in the cardiac catheterization of these patients, and to the photographic section of the Department of Medicine of the University of the Witwatersrand for the illustrations.

ADDENDUM

Since this paper was written, two interesting events have occurred in Case 4. First, while undergoing an external jugular venipuncture, the patient cried a great deal, became cyanotic, but developed a marked bradycardia (pulse rate of 40 per minute), which was presumably due to vagal stimulation. Her loud systolic murmur disappeared during the attack and the pupils were pin-point in size. By the time the electrocardiogram was available, the bradycardia had disappeared. Under certain circumstances a cyanotic spell may be accompanied by bradycardia instead of tachycardia—the remainder of the clinical picture being unchanged (Table II).

Secondly, during open-heart surgery the infundibulum developed "spasm" and caused the patient's arterial oxygen saturation to drop from 64 to 28 per cent. Ether anesthesia was introduced, and the arterial oxygen saturation rose to 44 per cent, with some visible movement of the infundibulum. The use of cyclopropane anesthesia, as recommended by Wood,[4] resulted in further relief of the infundibular obstruction, with a rise in arterial oxygen saturation to 66 per cent.

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Studies on Subjects With and Without Coronary Heart Disease. Serum Lipid, Lipoprotein, and Protein Determinations and Their Relation to Ballistocardiographic Findings (A Preliminary Survey)

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The purpose of this communication is to report the results of a preliminary survey of certain serum lipid-protein and circulatory measurements made on normal persons and patients with coronary heart disease. The reasons for this survey were threefold: (1) to determine whether any association exists between the measured variables and age, (2) to compare the findings in subjects with and without coronary disease, and (3) to look for relationships between the results of the circulatory (ballistocardiographic) and biochemical studies.

I. MATERIAL

This preliminary survey is based on the data obtained from 165 normal subjects and 115 patients with coronary heart disease (angina pectoris or remote myocardial infarction) from a larger group being studied periodically. The diagnostic criteria used in the selection of the individuals in these groups have been described elsewhere.[1,2] All patients in these two categories who were studied during a prescribed time period were included. The only subjects excluded were the relatively small number who were under treatment with low-fat, low-cholesterol diets or with estrogen preparations; the results obtained on them have been described elsewhere.[3,4] The normal persons ranged in age from 20 to 80 years, and the group included 117 men and 48 women. Patients with coronary heart disease ranged in age from 30 to 80 years; there were 95 men and 20 women (see Table I).

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This work represents the combined efforts of a research group which includes: Wm. R. Scarborough, Benjamin M. Baker, Jr., Samuel A. Talbot, Martin L. Singewald, Frank W. Davis, Jr., Robert E. Mason, Patricia M. Smith, and Salle A. Scarborough.

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II. METHODS

A. *Chemical Determinations.*—Blood was drawn at the conclusion of certain routine testing procedures and without regard to the time elapsed since the previous meal. Total cholesterol and protein-lipoprotein (electrophoretic) determinations were carried out on the same serum by persons who had no clinical information pertaining to the subjects being studied.

1. *Serum cholesterol:* Determinations of serum cholesterol were carried out by the routine chemical laboratory of The Johns Hopkins Hospital, using the Buell modification of the Sackett-Bloor method. This method has been in use since 1935, but the detailed procedure was published for the first time in a recent paper by Thomas and Eisenberg,[5] who studied the method's reliability.

2. *Paper electrophoretic patterns of proteins and lipoproteins:* The paper electrophoretic method, modified from Slater and Kunkel,[6] involved using Whatman #3 mm. filter paper in 0.06 ionic, pH 8.6 barbital buffer. Proteins were stained with brom-phenol blue, and lipoproteins were stained with 40 per cent ethanol saturated with oil-red-O. Concentrations of proteins and lipoproteins were estimated in comparison with patterns prepared simultaneously from pooled normal serum. The degree of departures from the normal for each fraction was graded, but aside from this no quantitative measurement was attempted.

B. *Other Tests.*—Other routine test procedures included the recording of 12-lead electrocardiograms, ballistocardiograms (Starr type), blood pressure, and, in most instances, a chest x-ray and a "cigarette test." The methods employed and the classification used are described elsewhere.[1,2]

C. *Method of Handling Data.*—Although multiple studies were carried out on many of the subjects, this preliminary survey is concerned only with the results of the first study on each subject during a prescribed time period.

The groups of individuals studied were not random samples, and since some of the measured variables are age-dependent, each group was divided into age-decades when comparisons were made between groups.

Of the various protein and lipoprotein electrophoretic fractions, only two, the alpha-2 protein and the beta lipoprotein, appeared to be altered with any frequency, and only these are included in the analysis. For the alpha-2 protein a definite increase in quantity and/or retarded migration was considered as an alpha-2 abnormality. For the beta lipoprotein, only an increased quantity was considered. The frequency with which such changes occurred was expressed in terms of percentage of the total number of subjects in each age group. The frequency of normal, borderline, and abnormal ballistocardiograms was similarly expressed as percentage of the total number of subjects in each age group.

Differences (d) in means or proportions were considered statistically significant if they were more than twice as large as the corresponding standard error, i.e., d/S.E. greater than 2.0. This corresponds to a probability (p) value of less than 0.05. However, for small samples (less than 30) the corresponding p value may be somewhat greater than 0.05.

The data were analyzed along the following lines: (1) Relationship of the measured variables to age in the various subject groups. (2) Comparison of the lipid-protein and ballistocardiographic results in groups of subjects with and without coronary heart disease, but comparable in age. (3) Relationship between ballistocardiographic wave form and serum lipids and/or proteins in patients with and without overt coronary disease. Specifically, we sought to determine whether serum lipid and/or protein abnormalities occurred with significantly greater frequency in individuals with abnormal ballistocardiograms than in those comparable in age but with normal records.

III. RESULTS

The age and sex distributions for the several study groups are shown in Table I. Those for the normal subjects are shown with and without the third decade.

With respect to age-frequency, the range of ages in patients with coronary heart disease was necessarily limited by the nature of the disease, but this group appeared to be distributed in a reasonably "normal" fashion, more so than were the normal subjects. Since comparisons between the two groups are made in comparable age-decades, normal age distribution is not a requisite.

The ratio of men to women in the whole normal control group was 2.4:1, and the proportion of women in various decades varied from 12 to 40 per cent, with an average of about 30 per cent. In the untreated patients with coronary heart disease, women constituted only 17 per cent of the sample, the male to female ratio being 4.8:1. The relatively small proportion of women in both groups, and the limited size of the whole sample made it unwise to attempt to segregate the sexes, so that the men and women were lumped together in the analyses.

TABLE I. PRELIMINARY SURVEY OF SERUM LIPID MEASUREMENTS IN NORMAL SUBJECTS AND IN PATIENTS WITH CORONARY ARTERY DISEASE (C.A.D.)

	<30 YR.	30-39	40-49	50-59	60-69	70-79	ALL AGES
Age Frequency Distribution							
C.A.D.							
n =	0	11	32	40	26	6	115
% of Total	0	9.6	27.3	34.2	22.2	5.1	100
Normals with third decade included							
n =	22	25	37	42	31	8	165
% of Total	13.3	15.2	22.4	25.4	18.8	4.9	100
Normals without third decade							
n =	—	25	37	42	31	8	143
% of Total	—	17.5	25.9	29.4	21.7	5.6	100
Sex Distribution by Age-Decade							
Normal							
Men							
n =	16	15	23	37	21	5	117
% of Decade Total	73	60	62	88	68	63	71
Women							
n =	6	10	14	5	10	3	48
% of Decade Total	27	40	38	12	32	37	29
C.A.D.							
Men							
n =	0	11	25	33	22	4	95
% of Decade Total	0	100	78	83	85	67	83
Women							
n =	0	0	7	7	4	2	20
% of Decade Total	0	0	22	17	15	23	17

Ratios—Normal M:F = 2.4:1. C.A.D. M:F = 4.8:1.

A. *Biochemical Measurements.*—

1. *Serum cholesterol:* In the *normal group* there was a definite age trend, with a progressive and linear rise in mean cholesterol values from the third to the sixth decades (see Fig. 1 and Table II). The values flattened off in the seventh and fell in the eighth decades. From age 20 to 59 the mean serum cholesterol rose 2.1 mg. per cent per year. The mean for the group as a whole was 255± 51 mg. per cent; the coefficient of variability was 20 per cent.

In the *patients with coronary artery disease* the decade means were in all cases higher than the corresponding means in the normal group, by 18 to 55 mg. per cent. An age trend in the patients was not so definite as in the normal subjects,

TABLE II

AGE DECADE	NO.	SERUM CHOLESTEROL (MEAN ± 1 S.D.)	INCREASED AND/OR RETARDED α2 PROTEINS		INCREASED β LIPOPROTEINS		ABNORMAL α2 AND/OR β		ABNORMAL BCGs	
			NO.	%	NO.	%	NO.	%	NO.	%
Normal Subjects										
<30	22	210 ± 32	0	0	2	9	2	9	0	0
30–39	25	235 ± 43	2	8	4	16	5	20	0	0
40–49	37	253 ± 44	5	14	7	19	9	24	3	8.1
50–59	42	274 ± 50	10	24	15	36	20	48	14	33.3
60–69	31	279 ± 48	6	19	12	42	15	48	21	67.8
70–79	8	260 ± 54	4	50	2	25	4	50	8	100.0
All Ages	165	255 ± 51	27	16	43	26	55	33	46	27.9
Patients With Coronary Artery Disease										
30–39	11	270 ± 86	3	27	5	45	6	55*	3	27.3
40–49	32	308 ± 77*	13	41*	21	66*	22	69*	15	46.9*
50–59	40	311 ± 70*	17	43	27	68*	33	83*	28	70.0*
60–69	26	308 ± 76	11	42	12	46	17	65	21	80.8
70–79	6	278 ± 63	2	33	3	50	3	50	6	100.0
All Ages	115	303 ± 76*	46	40*	68	59*	81	70*	73	63.5*
Normal Subjects										
40–69	110	269 ± 48	21	19	34	31	44	40	38	34.5
Patients With Coronary Artery Disease										
40–69	98	308 ± 75*	41	42*	60	61*	72	74*	64	65.3*
d/S.E.		4.4		3.7		4.5		5.3		4.7

*d/S.E. is over 2.0, and values are significantly different from comparable values in normal subjects.

possibly because of the limited age range. Nevertheless, there was an increase from the fourth to fifth decades and a decrease from the seventh to eighth decades paralleling changes in the normal group. Mean cholesterol for the coronary heart disease group as a whole was 303± 76 mg. per cent. Although the scatter of these values, in absolute terms, is greater than in the normal subjects, the relative scatter with respect to the mean is more comparable but is still higher; the coefficient of variability is 25 per cent. The higher mean and greater scatter of values in the coronary group could be due to the presence of a few individuals with unusually high values producing a skewed distribution. Table III and

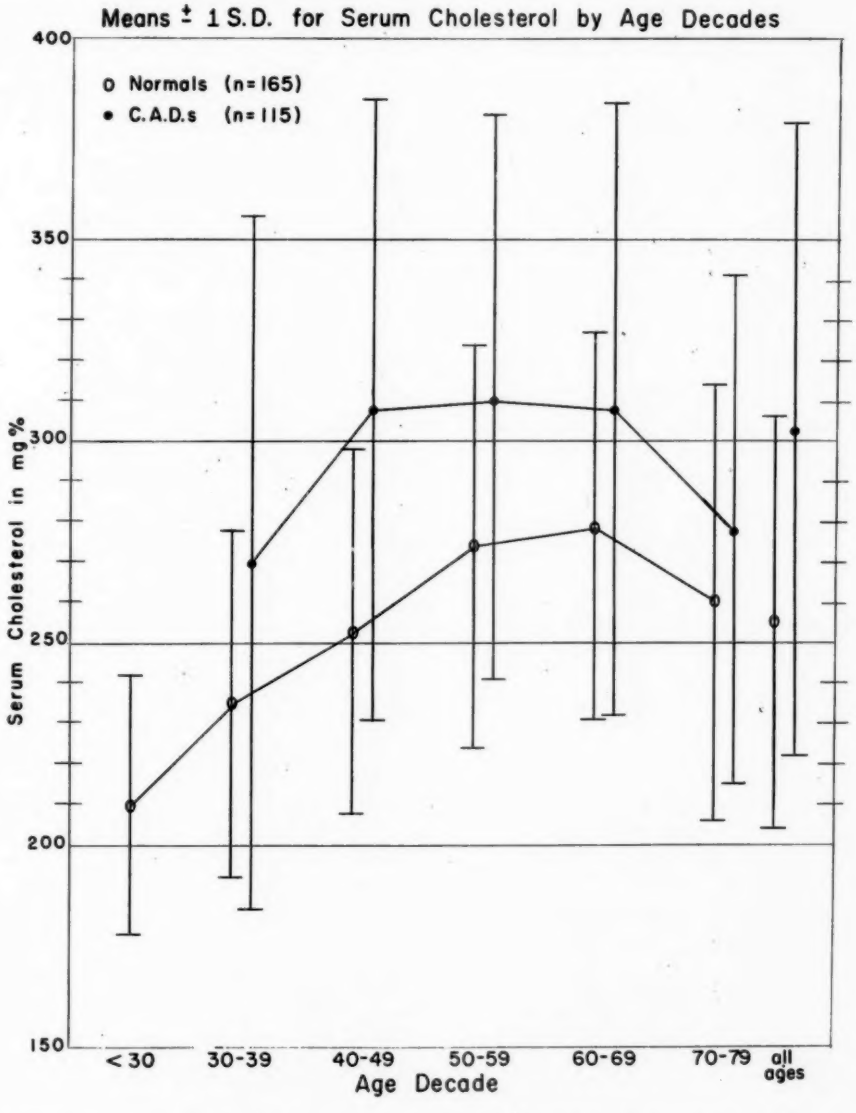

Fig. 1.—Mean total serum cholesterol by age decades. In this and all other illustrations, C.A.D. refers to coronary artery disease. Closed circles represent decade means in patients with coronary disease, and open circles represent the corresponding values in normal healthy persons. One standard deviation about each mean is shown. Corresponding means are significantly higher in coronary patients than in normal subjects in the fifth and sixth decades.

Fig. 2 show that although there is some skewing of this sort, there is also a general shift toward higher values in these patients when compared with the normal subjects. This shift is not appreciably different if subjects less than 30 years of age are excluded from the normal group.

The differences between the decade means of the normal subjects and the patients are statistically significant (that is, d/S.E. $>$ 2.0) only in the fifth and sixth decades. There were comparable numbers of patients with and without coronary heart disease in the fifth, sixth, and seventh decades. When these decades are combined, the mean serum cholesterol for the normal subjects is 269±48 mg. per cent, and for the coronary patients it is 308±75 mg. per cent. The difference between these two means, 39 mg. per cent, is statistically highly significant (d/S.E. = 4.4).

TABLE III. FREQUENCY DISTRIBUTION OF SERUM CHOLESTEROL (IN MG. %)

	TOTAL	100–149	150–199	200–249	250–299	300–349	350–399	400–449	450–499	500–549
					All Normals					
No.	165	1	21	57	55	23	8			
%	100.0	0.6	12.7	34.5	33.3	14.0	4.9			
					Normals ≦ 30 Years					
No.	143	1	12	46	53	23	8			
%	100.0	0.7	8.4	32.2	37.0	16.1	5.6			
					Patients With C.A.D.					
No.	115		6	18	39	32	6	7	3	4
%	100		5.2	15.6	33.9	27.8	5.2	6.1	2.6	3.5

2. *Serum proteins and lipoproteins:* In the *normal control group* there appeared to be age trends for abnormalities of alpha-2 protein, beta lipoprotein, and alpha-2 and/or beta lipoprotein (see Fig. 3 and Table II). The highest incidence of abnormality was for alpha-2 and/or beta, followed in order by beta lipoprotein and alpha-2 protein. The curve representing increased beta lipoprotein bears a striking resemblance to that for serum cholesterol (Fig. 3), in that it increases to a maximum in the seventh decade and then falls to a lower value in the eighth. The average values for the three fractions for the group as a whole are shown in Table II, but these are not very meaningful since they depend on the age-distribution of the sample. Between the third and seventh decades the incidence of elevated beta lipoprotein increases about 8 per cent per decade.

In the *coronary group* the three fractions show age trends resembling that for cholesterol, in that they increase with age to a maximum in the sixth decade

and then fall to lower values in the next two decades. As in the normal group, the highest incidence of abnormality occurs in alpha-2 protein and/or beta lipoprotein, the lowest in alpha-2 protein alone, with the beta lipoprotein fraction occupying an intermediate position. The shape of the alpha-2 curve bears a striking resemblance to that of the cholesterol curve.

In order to compare the values obtained in the coronary patients with those in the normal subjects, individuals in the 40 to 69-year age group were combined, since the number of subjects and age-distribution were comparable in these groups. The mean values for all three fractions are included in the lower part of Table II. For each fraction the incidence of abnormality was significantly higher statistically in the patients with coronary disease than in the normal

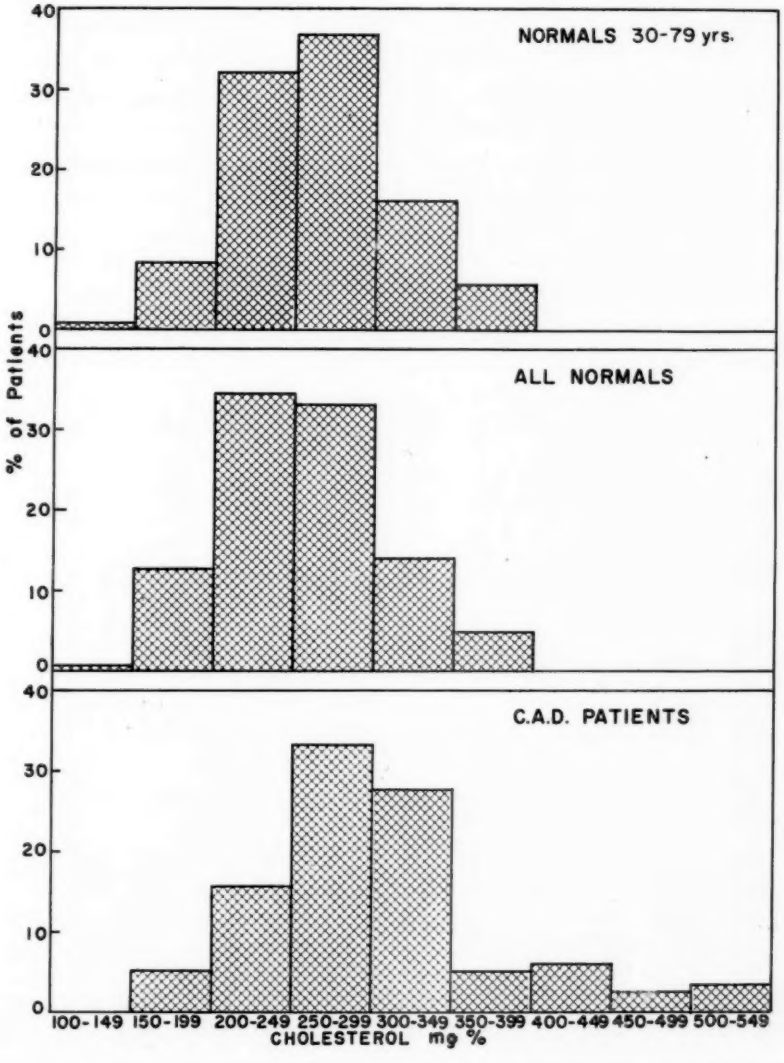

Fig. 2.—Frequency distribution of serum cholesterol values for normal subjects 30 or more years of age, for all normal subjects, and for all patients with coronary artery disease. In the latter group there is some skewing of the distribution at the upper end, but there is also a general shift toward higher values with respect to the normal subjects.

subjects. The level of significance was greatest for alpha-2 and/or beta (d/S.E. = 5.3), and somewhat lower for beta alone (d/S.E. = 4.5) and for alpha-2 alone (d/S.E.= 3.7).

When the coronary and normal subjects in each age-decade were compared, the differences were of a lower order of significance; this was due in part to the smaller numbers involved. Coronary patients showed a significantly higher incidence of abnormality of alpha-2 protein and/or beta lipoprotein in the fourth, fifth, and sixth decades. Increased beta lipoprotein was significantly more frequent in the fifth and sixth decades, as was alpha-2 in the fifth decade.

B. *Ballistocardiographic Measurements: (Table II and Fig. 4).*—

In the *normal group* the incidence of ballistocardiographic abnormality was strongly related to age. Below the age of 40 the ballistocardiogram was normal in all subjects, but was abnormal in 8, 33, 68, and 100 per cent of the subjects in the fifth, sixth, seventh, and eighth decades, respectively (see Fig. 4). In the age group from 40 to 69 years the ballistocardiogram was normal in 45 per cent, borderline in 20 per cent, and abnormal in 35 per cent.

In the *coronary group* the incidence of abnormal ballistocardiograms was higher than in comparable age-decades in the normal group, but a similar age

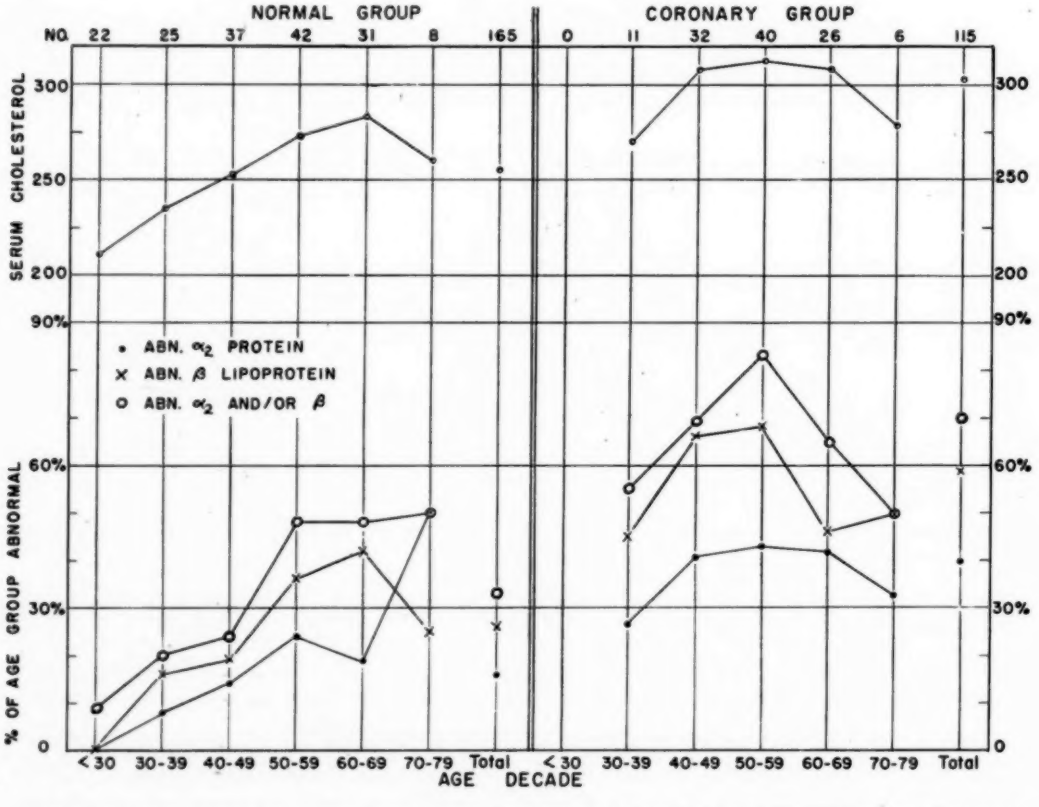

Fig. 3.—Mean serum cholesterol values and frequency of protein-lipid abnormalities by age-decade in "normal" and "coronary" groups. In the lower half of this illustration, closed circles represent alpha-2-protein abnormality (increased quantity and/or retarded migration) and crosses (x) relate to beta-lipoprotein abnormality (increased quantity). The open circles represent the proportion of individuals with one or both of these abnormalities. See text.

trend was also present. In the age range from 40 to 69 years the ballistocardiogram in these patients with coronary artery disease was normal in 18 per cent, borderline in 16 per cent, and abnormal in 65 per cent.

C. *Relation of Ballistocardiographic Abnormalities to Changes in Serum Lipids and/or Proteins.*—

These relationships proved difficult to determine because of the relatively small number of subjects and because the frequency of abnormality of the ballistocardiogram and of lipids and proteins was strongly related to age. The question here is whether abnormalities of serum lipids and/or protein occur more frequently in subjects with abnormal ballistocardiograms than in those with normal ballistocardiograms. Table IV, A and B shows such comparisons, with the subjects arranged in various age groups.

When the *normal subjects* are grouped to include all ages or all who are 40 or more years of age, serum lipid and/or protein abnormalities were (with one exception) significantly higher in subjects with abnormal ballistocardiograms than in those with normal records. However, it seems likely that this is due partly or wholly to age-dependence of both variables. This might be eliminated if the subjects were handled by age-decades, but the small number of *abnormal* records in the younger groups and of *normal* records in the older groups makes them

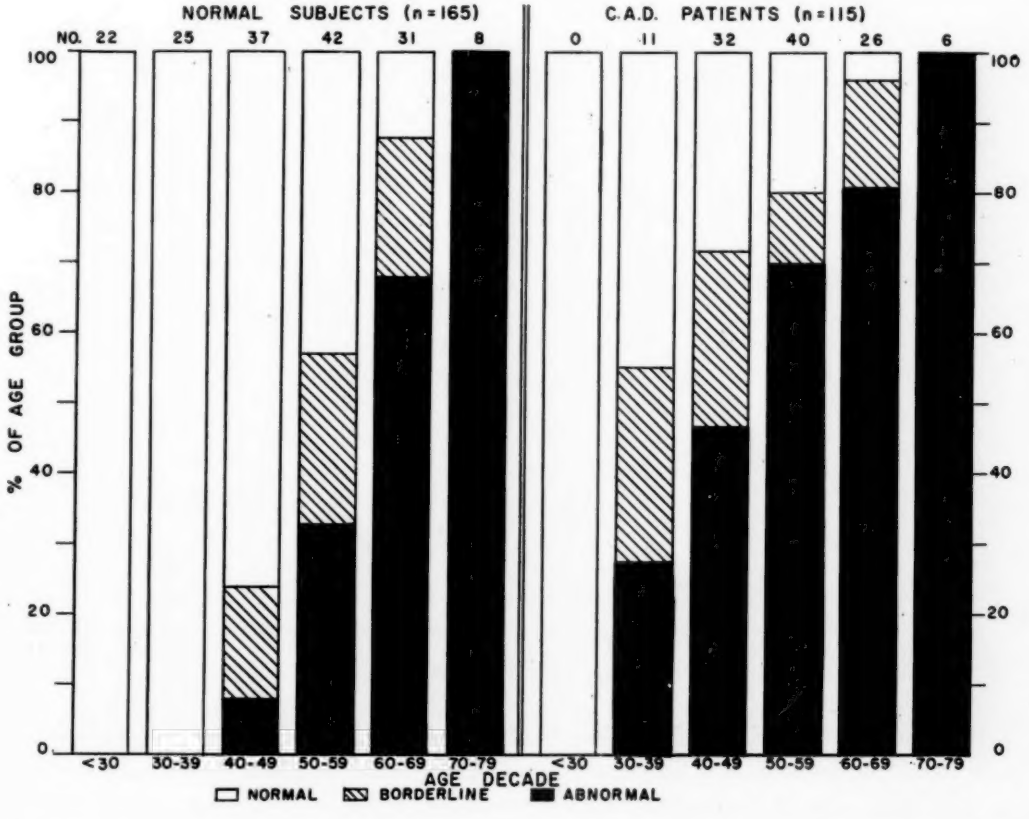

Fig. 4.—Bar diagram showing the proportion of individuals in each age-decade with normal, borderline, and abnormal ballistocardiograms. See text.

unsuitable for statistical treatment. In the sixth decade there are almost equal numbers of normal and abnormal ballistocardiograms, and the frequency of lipid-protein abnormalities is 33 per cent higher in patients with abnormal records than in those with normal records. This difference is of borderline significance; the standard error of this difference is high because of the small number (n = 32) of subjects in the group.

The *coronary patients* differed considerably from the normals. In the age group 40 to 79 years, abnormal alpha-2 protein was present in a significantly higher proportion of patients with abnormal ballistocardiograms, but this was not the case with the other fractions. On the other hand, in young patients with coronary artery disease, 30 to 49 years, all abnormal fractions were significantly more frequent in those with abnormal ballistocardiograms than in those with normal records, in spite of the fact that the group was small (n = 32).

TABLE IV, A. RELATION OF BALLISTOCARDIOGRAPHIC FORM TO SERUM LIPIDS AND PROTEINS (COMBINED GROUP 40-79 YEARS OF AGE)

	BCG WAVE FORM						DIFF. A-N† (%)	d/S.E.
	NORMAL		BORDERLINE		ABNORMAL			
	NO.	%	NO.	%	NO.	%		
Normal Group (40-79 Yr. Old)								
Total No. = 118	50	—	22	—	46	—	—	—
α2 Protein increased and/or retarded	6	12	7	32	12	26	14	1.75
β Lipoprotein increased	12	24	4	18	21	47*	23	2.4
Change in α2 and/or β	14	28	8	36	26	57*	29	3.0
Serum cholesterol	265		261		276		10.9	1.2
S.D.	47.6		48.3		49.0			
Coronary Group (40-79 Yr. Old)								
Total No. = 104	18	—	16	—	70	—	—	—
α2 Protein increased and/or retarded	2	11	4	25	37	53*	42	4.4
β Lipoprotein increased	13	72	10	63	40	57	−15	1.2
Change in α2 and/or β	13	72	9	56	53	76	4	—
Serum cholesterol	321		325		299		−22.1	1.1
S.D.	83.0		81.7		66.4			

*d/S.E. > 2.0; these values are significantly higher than those from subjects with normal ballistocardiograms.

†Difference between subjects with abnormal and normal ballistocardiograms.

Although there is a suggestion that abnormalities of the ballistocardiogram and of serum protein and lipoprotein are related, the evidence is not very strong.

In the *normal subjects*, serum cholesterol and the frequency of abnormal ballistocardiograms both increased with age. It is hardly surprising, therefore, that for the group as a whole, serum cholesterol was significantly higher in sub-

jects with abnormal ballistocardiograms than in those with normal records (Table IV,B). However, if the subjects under the age of 40, all of whom had normal ballistocardiograms, are excluded, and the analysis is confined to those from 40 to 79 years (Table IV,A), there is no significant difference between cholesterol levels in the individuals with normal and those with abnormal ballistocardiograms. The same is true of the *coronary disease patients* of all ages or of 40 to 79 years. However, the young patients (30 to 49 years) showed the same trends for cholesterol as for proteins and lipoproteins. A significantly higher mean cholesterol level was present in patients with abnormal ballistocardiograms than in those with normal records, but the difference (54 mg. per cent) was not highly significant.

TABLE IV, B

	BCG WAVE FORM						DIFF. A-N† (%)	d/S.E.
	NORMAL		BORDERLINE		ABNORMAL			
	NO.	%	NO.	%	NO.	%		
Normal Group (All Ages)								
Total No. = 165	97	—	22	—	46	—	—	—
α2 Protein increased and/or retarded	8	8	7	32	12	26*	18	2.6
β Lipoprotein increased	18	19	4	18	21	46*	27	3.2
Change in α2 and/or β	21	22	8	36	26	57*	35	4.2
Serum cholesterol	245		261		276*		30.9	5.3
S.D.	48.9		48.3		49.0			
Patients With C.A.D. (All Ages)								
Total No. = 115	23	—	19	—	73	—	—	—
α2 Protein increased and/or retarded	2	9	5	26	39	53*	44	5.2
β Lipoprotein increased	14	61	11	60	43	59	−2	—
Change in α2 and/or β	14	61	11	60	56	77	16	1.4
Serum cholesterol	299		312		302		2.6	0.1
S.D.	86.2		82.8		69.0			
Patients With C.A.D. (30-49 Yr.)								
Total No. = 43	14	—	11	—	18	—	—	—
α2 change	2	14	4	36	10	56*	42	2.8
β change	6	43	6	55	14	78*	35	2.1
α2 and/or β change	6	43	7	63	15	83*	40	2.5
Serum cholesterol	262		315		316*		54.0	2.3
S.D.	68.2		101.0		66.3			

*d/S.E. > 2.0; these values are significantly higher than those from subjects with normal ballistocardiograms.

†Difference between subjects with abnormal and normal ballistocardiograms.

IV. DISCUSSION

Several excellent studies on large numbers of subjects have been carried out recently relating to certain lipid, lipoprotein, and protein fractions of the serum and their changes with age and in atherosclerotic disease states. The study reported here was designed only to characterize the findings in small population samples from larger groups of persons with and without coronary heart disease who are under investigation here. Even though these samples were small, the results of the lipid measurements appear to be quite similar to those from larger studies. The changes in *serum cholesterol* with age in normal subjects observed in this survey were generally similar to the results obtained on large groups of normal men by Keys and associates,[7] Barker,[8] Jones and associates,[9] Lawry and associates,[10] and by the Cooperative Study on Lipoproteins and Atherosclerosis.[11] These investigators all found that mean serum cholesterol in men increased steadily to a maximum at about the age of 50, after which it decreased. Disregarding the absolute level of serum cholesterol, our results differed only in that after the age of 40 our values rose to higher levels and the fall-off occurred later. The Cooperative Study Group observed that the changes with age in women differed from those in men. In women between 20 and 40 years, mean serum cholesterol rose more gradually, and above this age it continued to rise, reaching a level considerably higher than in men at the age of 60. Inasmuch as women constituted approximately 30 per cent of our normal group, this could explain the relatively higher values above the age of 50. It seemed unwise to treat women separately because they were few in number and distributed over a rather broad age range (six decades).

The rate of rise in cholesterol over the first few decades in our normal subjects was about 2.1 mg. per cent per year. This is in agreement with results obtained by Keys (2.2 mg. per cent per year),[7] the Cooperative Study Group (2.5 mg. per cent per year),[11] Gertler and associates (2.0 mg. per cent per year),[12] and Thomas and Eisenberg (2.8 mg. per cent per year).[5] Although not universal,[13-16] an increase in cholesterol with age has been a frequent finding. This does not necessarily indicate that cholesterol rises as a normal individual grows older. In fact, Sperry and Webb[13] and Man and Peters[14] determined the serum cholesterol on the same individuals after a lapse of 10 to 20 years and found little or no change. However, the number of subjects they studied was small, and interpretation of the data was rendered difficult because some of the subjects were in the age range in which serum cholesterol normally levels off. In any case, the cross-section studies suggest rather strongly that there is a definite association between age and serum cholesterol. It is not certain why serum cholesterol in men levels off and falls in the older age groups, but it has been suggested that this may be due to the fact that the individuals with high cholesterol developed coronary disease or died and, therefore, were not represented in the normal group.

The higher values for serum cholesterol in patients with coronary disease and the overlap of the values for subjects with and without coronary disease observed in this study are too well known to require documentation. The coronary group in this study was composed of individuals with either angina pectoris or old myocardial infarction, or both; they were not treated separately because

either condition is believed to constitute good evidence for the presence of coronary atherosclerosis. The decade means for serum cholesterol were consistently higher in the coronary patients, and there was an apparent age trend resembling that in normal subjects. However, it is the fourth and eighth decades which are responsible for this trend, and the number of patients in these two decades is rather small. Nevertheless, the results agree rather well with those obtained by Gertler and co-workers,[12] who studied normal subjects and patients who had had myocardial infarction. In contrast, Lawry and her colleagues[10] found different age trends for cholesterol in patients with angina pectoris and in patients with old myocardial infarction. In the latter there was a progressive fall from 35 to 65 years of age, whereas the changes with age in patients with angina pectoris were an exaggeration of the similar age trend observed in normal men and were thus similar to the results of the present study.

Attention has already been called to the fact that the frequency distribution of cholesterol values in the normal subjects was reasonably normal, whereas in the patients with coronary disease there was some skewing at the upper end (Fig. 2 and Table II). In the latter group, 20 individuals had values exceeding 350 mg. per cent; only one of these had diabetes mellitus and none of them had xanthomatosis, nephrosis, or myxedema. Only 31 of 165 (18.8 per cent) normal subjects had values above 300 mg. per cent, but 52 of 115 (45.2 per cent) patients with coronary disease had values higher than this level. The mode in the normal subjects was 200 to 299 mg. per cent, and in the coronary patients it was 250 to 350 mg. per cent.

The changes in the frequency of elevated *beta lipoproteins* with age and in the presence of coronary artery disease agree, in general, with the results of more extensive studies in which more refined methods were used. In the normal subjects in this study there was a progressive increase to a maximum incidence of 42 per cent in the seventh decade, followed by a fall in the eighth decade; in this respect, the decade mean curve (Fig. 3) resembles that for cholesterol. In patients with coronary disease this does not appear to be the case. Elevated beta lipoproteins were found in a considerably higher proportion of patients with coronary disease than in normal subjects, and all decade means in the former were greater than all decade means in the normal subjects. For corresponding age-decades the differences proved significant (p less than 0.05) only in the fifth and sixth decades.

Paper electrophoretic studies of *serum proteins* revealed that the most frequent alteration was in the alpha-2 globulin, which was either increased in quantity or retarded in migration, or both. All changes of this sort were lumped together and termed "alpha-2 abnormalities." These abnormalities occurred somewhat less frequently than did elevated beta lipoproteins, but there were similar trends with age and in coronary disease (Fig. 3). In the final analysis the proportion of subjects in each decade with abnormality of either beta lipoprotein or alpha-2 protein, or both, were determined, and this yielded somewhat higher proportions than either of the two alone. Combining the protein and lipoprotein abnormalities in this manner would seem somewhat arbitrary, but some justification is provided by results obtained by Barr, Russ and Eder,[17,18] in 1951.

They carried out studies on human plasma, using the Cohn protein microfractionation method 10. It was found that the protein in fractions C (Cohn's Fraction III_0) and D (Cohn's Fractions $I + III_{1,2,3}$) was increased in patients with atherosclerosis (coronary disease, in most cases) as compared with clinically normal persons, and it was also greater in older than in younger normals. They found that part of the increase in protein in Fractions C and D was due to an increase in beta lipoprotein, and that part of it was due to an increase in alpha-2 globulin (and fibrinogen). Only 2 of 33 atherosclerotic patients failed to show some abnormality in proteins or lipoproteins. This provides some rationale for combining protein and lipoprotein abnormalities as we did in this study. Unusually large alpha-2 fractions have been observed in certain elderly persons by Ackermann and co-workers,[19] who used zone electrophoresis on a starch medium. With paper electrophoresis, Pollak[20] found, in patients with recent myocardial infarction, rather characteristic alterations in pattern, and the major changes included an increase in alpha-2 globulin, alpha-2 glycoprotein, and total globulin, and a decrease in albumin and total cholesterol. In patients with angina pectoris but without recent infarction, alterations in the pattern were not sufficient to distinguish them from healthy persons. Leinwand and Moore[21] and Jenckes and associates[22] have observed increased alpha-2 globulin in some patients with various atherosclerotic diseases. It should be noted that none of our patients with coronary artery disease had had recent myocardial infarction, and in all cases with a history of infarction, at least 6 weeks had elapsed since its onset. Although a great many studies have been carried out on the lipoproteins in atherosclerotic disease, there is much less information on the alterations in serum proteins. Furthermore, differences in electrophoretic techniques and methods of analysis make it somewhat difficult to compare the results with ours.

One of the most important aspects of this study was the search for possible relationships between abnormal alterations in serum lipids and proteins and those in circulatory function as reflected by the ballistocardiogram. The reason for the rapidly increasing frequency of abnormal ballistocardiograms from clinically normal persons from the age of 40 onward is still uncertain. It seems safe to assume that virtually all persons above 40 have some degree of coronary atherosclerosis, and it is in these individuals that clinical coronary disease manifests itself so frequently. Nevertheless, there is no direct proof that subclinical coronary disease is responsible for the development of abnormal ballistocardiograms in older normal persons. It has been convincingly demonstrated that lipid-protein abnormalities are more frequent in patients with coronary disease than in normal persons and that they tend to increase with age[9,11]; our results agree well with these observations. Furthermore, lipid-protein abnormalities were found to be more frequent in normal individuals who eventually developed overt coronary disease than in those who remained healthy.[23] Therefore, if it could be shown that lipoprotein abnormality is more frequent in subjects with abnormal ballistocardiograms than in those with normal ones, this should strengthen the conviction that individuals with abnormal records are more likely to have, or to develop, coronary heart disease than are those with normal ballistocardiograms. Interpretation of our data was made difficult because of the apparent

relationship of lipid-protein and ballistocardiographic abnormalities with age; this age-association was especially strong for ballistocardiographic abnormality in both the coronary and normal groups and for lipid-protein abnormality in the normal group. Furthermore, the data did not lend themselves to either first-order or partial correlations, and for this reason, comparisons were necessarily restricted to small groups which were comparable in age. In spite of these difficulties there was a suggestive trend toward association of ballistocardiographic and lipid-protein abnormalities, especially in the normal group; lipid-protein abnormalities were considerably more frequent in subjects with abnormal ballistocardiograms than in those with normal ones. The results in the coronary patients depended on the age grouping. In the whole coronary group and in those 40 to 79 years of age, alpha-2 globulin was abnormal in a much higher proportion of patients with abnormal ballistocardiograms than in those with normal records. This was not the case for beta-lipoprotein or for alpha-2 and/or beta-lipoprotein abnormalities; these were quite frequent regardless of the classification of the ballistocardiographic wave form. On the other hand, in young patients with coronary disease (30 to 49 years), all of the lipid-protein abnormalities were significantly greater in those with abnormal ballistocardiograms. The reason for these unusual relationships is unclear at present, but the results obtained thus far demand further exploration. The significance of alterations in alpha-2 protein should be of particular interest.

In normal individuals, no association was found between ballistocardiographic wave form and serum cholesterol level, aside from their mutual relation to age, and this agrees with results obtained by Taylor and Anderson.[24] Similarly, there was no association of the two in coronary patients of all ages or in those over 40, but the mean serum cholesterol was significantly higher in young patients (30 to 49 years) with abnormal ballistocardiograms. Engelberg[25] recently compared the ballistocardiographic findings with serum cholesterol and lipoprotein (Atherogenic Index) levels in a large group of subjects. In 349 normal individuals there was a suggestive relationship between the degree of ballistocardiographic abnormality (in the resting state) and elevation of serum lipids, especially in those under the age of 50, but whether this is statistically significant cannot be determined from the published data. There appeared to be a somewhat stronger correlation between the classification of the postexercise ballistocardiogram and serum lipid and lipoprotein levels. However, as in our data, there were many instances in which elevated lipids were found when the ballistocardiogram was normal, and vice versa.

V. SUMMARY

1. Biochemical and ballistocardiographic studies were carried out on 115 ambulatory patients with coronary heart disease (angina pectoris, old myocardial infarction, or both) and 165 clinically normal subjects. Biochemical studies included determinations of total cholesterol, and paper electrophoretic studies of serum proteins and lipoproteins. Electrophoretic patterns were compared with simultaneously run patterns from pooled normal serum, and the departures

from normal were graded as to concentration and migration rate. Ballistocardiograms were of the Starr type and were classified as normal, borderline, and abnormal.

2. Mean serum cholesterol in the normal group rose progressively from age 20 to a maximum in the seventh decade, after which it fell. Cholesterol values were significantly higher in patients with coronary heart disease, but there was an age trend which resembled that in normal subjects.

3. The most significant changes in the protein and lipoprotein electrophoretic patterns were increased beta lipoprotein and increased and/or retarded alpha-2 protein. These alterations were treated separately and then combined as abnormalities of beta lipoprotein, alpha-2 protein, or both. In normal individuals these abnormalities increased in frequency with age, and in the sixth to eighth decades, one or more lipid-protein abnormalities were present in about 50 per cent of the subjects. In patients with coronary disease there was a suggestive age trend, though less marked than in normal subjects. The lipid-protein abnormalities in these patients were considerably more frequent than in the normal subjects especially over the age range from 30 to 59 years.

4. The ballistocardiogram was normal in all clinically normal persons under 40, but thereafter abnormal records occurred with increasing frequency to a maximum of 100 per cent in the eighth decade. Abnormal ballistocardiograms were more frequent in patients with coronary disease, but a similar age trend was observed.

5. Aside from their mutual relationship to age, no association could be found between serum cholesterol level and ballistocardiographic classification in normal individuals. Among patients with coronary disease, only in those from 30 to 49 years of age was mean serum cholesterol significantly higher in subjects with abnormal ballistocardiograms than in those with normal records. Lipoprotein and protein electrophoretic abnormalities were more frequent in normal subjects and young patients (30 to 49 years) with coronary heart disease whose ballistocardiograms were abnormal than in those whose records were normal.

6. The results of this study suggest that further exploration of the relationship between changes in serum lipid proteins and circulatory function may be rewarding.

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Pressure Pulse Waves in the Right Ventricle: Alteration in Patients With Pulmonic Stenosis and Pulmonary Hypertension

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The right ventricular pressure pulse reflects the volume of the right ventricular outflow, the resistance at the pulmonary valve, and the resistance of the pulmonary arterial tree. It may be distorted by various pathologic situations, the distortion reflecting the nature of the pathology. Bouchard and Cornu[1] reported the difference they noted between the contours of the right ventricular pressure tracings from patients with pulmonic stenosis and intact ventricular septum (hereafter called pulmonic stenosis) and those from patients with pulmonic stenosis and a ventricular septal defect (hereafter called tetralogy of Fallot). It is the purpose of this paper to present a more detailed analysis of this difference, and to show the characteristic change in contour produced by pulmonary hypertension.

METHODS AND MATERIALS

In 33 patients with pulmonic stenosis the diagnosis was considered to be sufficiently well established for inclusion of them in this report. To be included in this group each case had to fulfill at least one of the following criteria in addition to the clinical diagnosis: (1) neither left-to-right nor right-to-left shunt, (2) anatomic confirmation at surgery* or autopsy, (3) definite clinical improvement following pulmonary valvotomy. For inclusion in the group with tetralogy of Fallot each case had to fulfill at least one of the following criteria in addition to the clinical diagnosis: (1) cardiac catheter passed from the right ventricle directly into the aorta, (2) left-to-right shunt at the ventricular level, (3) definite clinical improvement following subclavian-pulmonary or aorticopulmonary anastomoses. By these standards there were 15 proved cases of tetralogy of Fallot and 18 proved cases of pulmonic stenosis. All tracings were recorded through a standard Cournand-type cardiac catheter during routine right heart catheterization or via a small plastic catheter inserted directly into the right ventricle at the time of surgery, using a Lilly capacitance type of electromanometer with a speed of response more than adequate for the analyses reported here.[2] Twenty-three measurements on 21 patients with left-to-right intracardiac shunts and pulmonary hypertension proved by direct measurement of the pulmonary arterial pressure are also reported. Fourteen of these patients had ventricular septal defects, 4 had the atrioventricularis communis syndrome, and 3 had patent ductus arteriosus.

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*One patient with an infundibular stenosis revealed a small ventricular septal defect at the time of direct exploration of the right ventricle, only after infundibular tissue had been resected. Since the right ventricular pressure at the time the tracing was made was 150/—10 as compared to 94/76 mm. Hg systemic pressure, and there was no evidence of increased oxygen content in the right ventricle, the case is classified functionally with the pulmonic stenosis group.

RESULTS

All patients classified as having tetralogy of Fallot had right ventricular pulse curves that were in all respects identical in contour to the normal right ventricular pulse curve except for elevated pressure. The shape can best be described as an inverted U (see Fig. 1). The right ventricular pressure tracings from the group having pulmonic stenosis show a definite distortion of the curve (see Fig. 2), with a gradual upslope to a sharp peak, followed by a slow descent to the diastolic level, i.e., an inverted V. In the tetralogy of Fallot group, the upslope duration averaged 21 per cent (expressed as per cent of the duration of the systolic pulse wave), ranging from 13 to 29 per cent, whereas the downslope duration averaged 25 per cent, with a range of 9 to 37 per cent. The pulmonic stenosis group had an upslope of 54 per cent (range, 27 to 62 per cent), with a downslope averaging 53 per cent (range, 38 to 73 per cent). There is virtually no overlap between the two groups.

Twenty-one of the 23 tracings from the right ventricle from 21 patients with pulmonary hypertension show an initial rapid upslope, followed by a more gradual rise to a peak, then followed by a rapid descent to the diastolic level, giving the gabled contour seen in Fig. 4. The two exceptions were tracings recorded from two of the patients with patent ductus who were recatheterized approximately one year after ligation of the ductus. Pulmonary hypertension persisted in both, but the right ventricular pulse pressure curve showed a distorted flat-topped contour.

DISCUSSION

A review of right ventricular pressure curves reproduced in various reports[3-12] may be summarized as follows: twenty-four of twenty-five patients (authors' diagnoses accepted as correct) with pulmonic stenosis showed the inverted V contour. Ten of twelve patients reported as having tetralogy of Fallot showed the inverted U type of curve.

Fineberg and Wiggers[13] progressively occluded the pulmonary artery in dogs and obtained right ventricular pressure tracings of the inverted V type. They ascribe the over-all changes as being due to right ventricular fatigue, but do not discuss the specific changes in contour. We have noted the same changes in contour in patients with intact ventricular septa who have small gradients across the pulmonary valve (see Fig. 3) and no signs of right ventricular fatigue.

When there is an adequate pressure outlet from the right ventricle, whether this be through a normal valve or through a ventricular septal defect, the contour of the right ventricular pressure wave is normal, independent of the height of the pressure. When there is inadequate outlet from the right ventricle, even relatively mild obstruction, the right ventricular pressure wave is distorted into the inverted V shape. The contour of the curves from the patients with pulmonary hypertension is a combination of both types of curves. The initial rapid upslope indicates that the outlet through the pulmonic valve and into the hilar vessels is adequate. The later slow upslope is indicative of the obstruction to flow offered by the narrowed pulmonary arterioles. Hypertrophy of the crista ventricularis may also be a factor in the contour distortion.

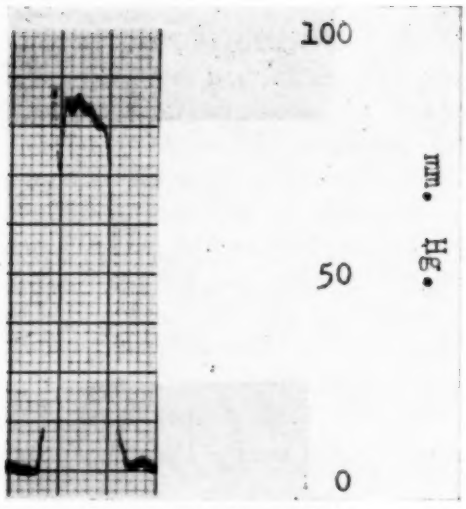

Fig. 1.—Tetralogy of Fallot.

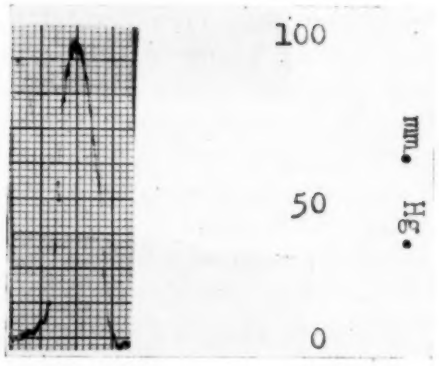

Fig. 2.—Pulmonic stenosis.

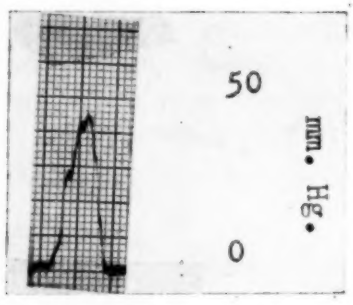

Fig. 3.—Mild pulmonic stenosis.

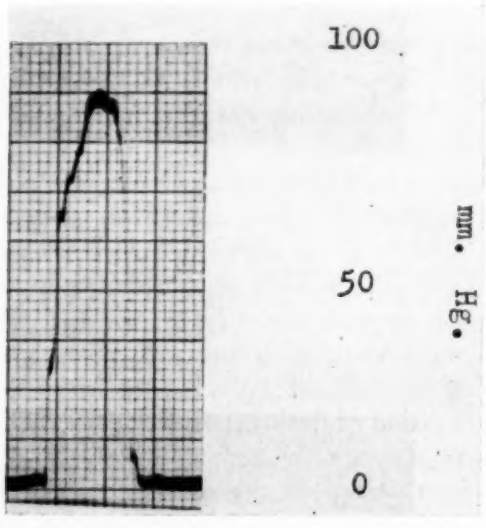

Fig. 4.—Pulmonary hypertension.

Widespread use of open cardiotomy with extracorporeal circulation will allow more complete anatomic correction of these lesions, using essentially the same surgical approach. In many instances, particularly in the cyanotic infant, valvotomy for pulmonic stenosis, some form of systemic-pulmonic anastomosis for tetralogy of Fallot, or some entirely different procedure for pulmonary hypertension, will be required. These varied surgical techniques necessitate accurate preoperative diagnosis. In this regard, the data obtained from analysis of the right ventricular pulse wave may be very valuable, particularly when the cardiac catheter cannot be advanced into the pulmonary artery.

SUMMARY

Fifteen patients with proved pulmonic stenosis with ventricular septal defect (tetralogy of Fallot) demonstrated right ventricular pressure pulse contours of the normal inverted U shape with elevated pressure (Fig. 1).

Eighteen patients with proved pulmonic stenosis with intact ventricular septum (pulmonic stenosis) demonstrated right ventricular pressure pulse contours of an inverted V shape (Fig. 2).

Twenty-one patients with proved pulmonary hypertension showed a gable-type contour of the right ventricular pressure pulse wave (Fig. 4). Two of these patients demonstrated this contour prior to ligation of a patent ductus arteriosus. Postoperatively, the contour was no longer typical.

The use of this observation as an aid in diagnosis, and the mechanisms involved in the production of these changes in contour is discussed.

I wish to thank Dr. Rachel Ash, Dr. Sidney Friedman, and Dr. Peter Vanace for advice and aid.

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Spatial Patterns of Ventricular Repolarization in Arterial Hypertension

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The known quantitative errors of conventional electrocardiography, such as those deriving from dipole location, torso shape, and different lead strength,[1-6] limit the usefulness of this classic method of investigation mainly to qualitative information. The several studies which have been carried out in the past with uncorrected leads to analyze magnitude and direction of the cardiac vectors either on the frontal plane or in space are not truly meaningful quantitatively.

The recent introduction into electrocardiographic research of more accurate systems for determining three orthogonal components of the human equivalent heart dipole, and correcting for the conventional errors,[6-9] enables quantitative spatial analysis of electrocardiographic potentials to be carried out with sufficient accuracy.[10,11] In recent times, there has been an increasing trend in the literature to apply these methods to physiologic and clinical observations, using both scalar and vectorial display.[8-21]

We have thought that this kind of approach might provide very useful information, particularly in such conditions as those characterized by a gradual development of a pathologic change, which seem ideal for quantitative evaluation. The heart involvement in arterial hypertension lends itself suitably to such an investigation: magnitude and duration of increased pressor values, and the absence or occurrence of complications are generally paralleled by electrocardiographic patterns which range from no pathologic signs to so-called left ventricular hypertrophy, up to the severest signs of systolic ventricular overload and strain. However, fruitful information will result only from a careful search for significant quantitative data. Since repolarization processes are more liable to be altered in arterial hypertension, magnitude and direction of the spatial T-wave vectors have seemed worthy of particular attention. It has been thought also that a study of the relationship between spatial depolarization and repolarization areas might provide information on electrocardiographic changes which may not be apparent on conventional leads. The existence of such a relationship, an issue strictly related to the often used and equally controversial concept of ventricular gradient,[22-26] is not clear from the preceding studies, and indeed could not be assessed from pure qualitative work. Therefore, our study on hypertensive subjects

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has been preceded by a thorough investigation of the spatial QRS and T-wave vectors, and of their relationships in a convenient series of normal subjects.

It can be anticipated that: (1) a significant correlation has been found to exist in normal subjects between spatial QRS- and T-wave areas, and between the angle (dA°) delimited by spatial QRS and T vectors and T magnitude; (2) the correlation between spatial QRS- and T-area magnitude decreases from normal subjects to hypertensive patients, paralleling severity of heart involvement; (3) the angle (dA°) between spatial QRS- and T-wave vectors increases progressively from normal subjects to severely hypertensive patients, the repolarization vector moving from its normal direction (leftward, downward, and frontward) to an entirely new position in space (rightward, upward, and frontward) when severe systolic overload is present; (4) the correlation between the angle (dA°) and T magnitude is completely lost even in those hypertensive subjects who do not show any change in repolarization on conventional electrocardiographic leads.

MATERIAL AND METHODS

Our observations have been carried out on 26 normal subjects, mostly medical students, and on 36 hypertensive patients. Only patients showing systolic blood pressure above 200 mm. Hg, and diastolic pressure above 110 mm. Hg were taken into consideration. Therefore, our pathologic population was comprised of cases of moderate, severe, and malignant hypertension. The patients were arranged into two separate groups, on the basis of conventional electrocardiographic patterns. Group I included all subjects (21) whose electrocardiogram showed no evident signs of altered repolarization, the conventional patterns either appearing normal or showing modifications of the QRS complex only (so-called left ventricular hypertrophy: increased amplitude of the QRS complex, slight delay of the intrinsicoid deflection). Group II included only subjects (15) showing altered repolarization: the conventional electrocardiographic patterns were those defined as left ventricular overload or strain. Only the tracings of those patients whose rate was between 70 and 90 were analyzed.

Corrected orthogonal electrocardiography was performed utilizing Frank's seven-electrode system,[9] which appears to combine simplicity of execution with proved accuracy.[10,11] Electrodes were located on the back of the neck, on the left leg, and on the thorax at the fifth intercostal level at the sternum. The five thoracic leads were in the frontal and posterior midline, right and left midaxillary lines, and at an angle of 45 degrees between the frontal midline and the left midaxillary line. Resistance networks were as calculated by Frank,[9] with the modifications appropriate for the input impedance of our recording system (Sanborn Viso-Cardiette). The polarity of the leads was such that upward (positive) deflections in the X lead (horizontal component) represented vectors directed to the left, whereas upward deflections in the Y lead (vertical component) indicated vectors directed downward; upward deflections in the Z lead (anteroposterior component) represented vectors directed posteriorly.

Scalar was preferred to vectorial display, mainly because of the better evaluation of the repolarization processes afforded by the former technique. Closer uniformity of electrocardiographic patterns with scalar recording, as compared to the variable configurations of vectorial loops, even in normal subjects, has been another criterion for selection of scalar display, at least in this first stage of our analysis. The time integrals of the QRS complex and of the T wave (beginning from the end of the S deflection: J point) were taken as measures of the depolarization and repolarization processes, respectively. As has been done frequently in conventional electrocardiography, these areas have been considered to have vectorial properties, and will be referred to throughout this paper as QRS- and T-area vectors. To measure these area vectors, the corrected electrocardiographic potentials, as recorded with the Viso-Cardiette, were photographed and, subsequently, with the aid of an enlarger, traced on standard paper, where they were measured

with a compensating planimeter. Values from each lead, expressed as μVsec, were adequately plotted, and the magnitude and direction of both area vectors were calculated on horizontal, frontal, and sagittal planes. Magnitude of the spatial vectors and the angie between the two (dA°), as well as spatial ventricular gradient magnitude and direction, were calculated according to trigonometric standards.[21] When necessary, statistical analysis was performed with current methods.[27]

RESULTS

Normal Subjects.—The observations in normal subjects are schematically presented in Fig. 1, and summarized in Table I. In agreement with previous reports utilizing corrected orthogonal leads,[13-15,17-19,28] it has been seen that the QRS-area vector is directed leftward, downward and posteriorly, whereas the direction of the T-wave area vector is leftward, downward and frontward. The angles between the QRS- and T-area spatial vectors (dA°) average 51 degrees (s = 22), their frequency distribution showing a peak between 30 and 60 degrees (Fig. 2,*A*).

TABLE I. SPATIAL QRS- AND T-AREA VECTORS IN NORMAL AND HYPERTENSIVE SUBJECTS (MEAN VALUES AND STANDARD DEVIATIONS)

	NORMAL SUBJECTS	HYPERTENSIVE PATIENTS (GROUP I)	HYPERTENSIVE PATIENTS (GROUP II)
QRS direction (degrees)			
horizontal	+ 24 ± 23	+ 33 ± 19	+ 34 ± 17
frontal	+ 40 ± 15	+ 16 ± 29	+ 17 ± 15
sagittal	+ 67 ± 27	+ 21 ± 40	+ 29 ± 23
T direction (degrees)			
horizontal	− 37 ± 17	− 66 ± 23	−116 ± 20
frontal	+ 41 ± 16	+ 50 ± 28	−156 ± 53
sagittal	+131 ± 19	+151 ± 22	−174 ± 23
QRS magnitude (μVsec)			
horizontal	28.1 ± 12.5	56.1 ± 20.0	72.6 ± 19.3
frontal	30.7 ± 11.8	53.2 ± 18.6	62.5 ± 17.9
sagittal	25.3 ± 13.9	38.6 ± 18.6	54.0 ± 28.7
T magnitude (μVsec)			
horizontal	30.8 ± 15.5	37.9 ± 16.7	49.1 ± 16.5
frontal	32.3 ± 13.1	24.4 ± 15.3	27.2 ± 15.9
sagittal	29.3 ± 15.5	38.2 ± 19.5	45.4 ± 17.7
Spatial QRS magnitude (μVsec)	35.0 ± 14.1	62.3 ± 20.4	78.1 ± 23.1
Spatial T magnitude (μVsec)	38.4 ± 17.2	42.4 ± 19.3	52.7 ± 16.6
dA° (degrees)	51.0 ± 22.0	91.0 ± 27.0	141.0 ± 21.0
Spatial ventricular gradient direction (degrees)	27.0 ± 14.0	30.0 ± 12.0	37.0 ± 24.0
Spatial ventricular gradient magnitude (μVsec)	53.6 ± 18.2	75.1 ± 27.4	51.8 ± 30.1

Mean QRS- and T-area vector magnitudes on the different planes are reproduced in Table I. Mean spatial QRS- and T-area vector magnitudes are not markedly different, measuring 35.0 μVsec (s = 14.1) and 38.4 μVsec (s = 17.2), respectively.

Spatial ventricular gradients, vectorially calculated from spatial QRS and T areas, average 53.6 μVsec (s = 18.2) in magnitude, the mean angle delimited by the QRS and gradient vectors being 27 degrees (s = 14.0).

When the magnitudes of the spatial QRS areas versus the magnitudes of the spatial T areas were plotted, a highly significant correlation was found, with

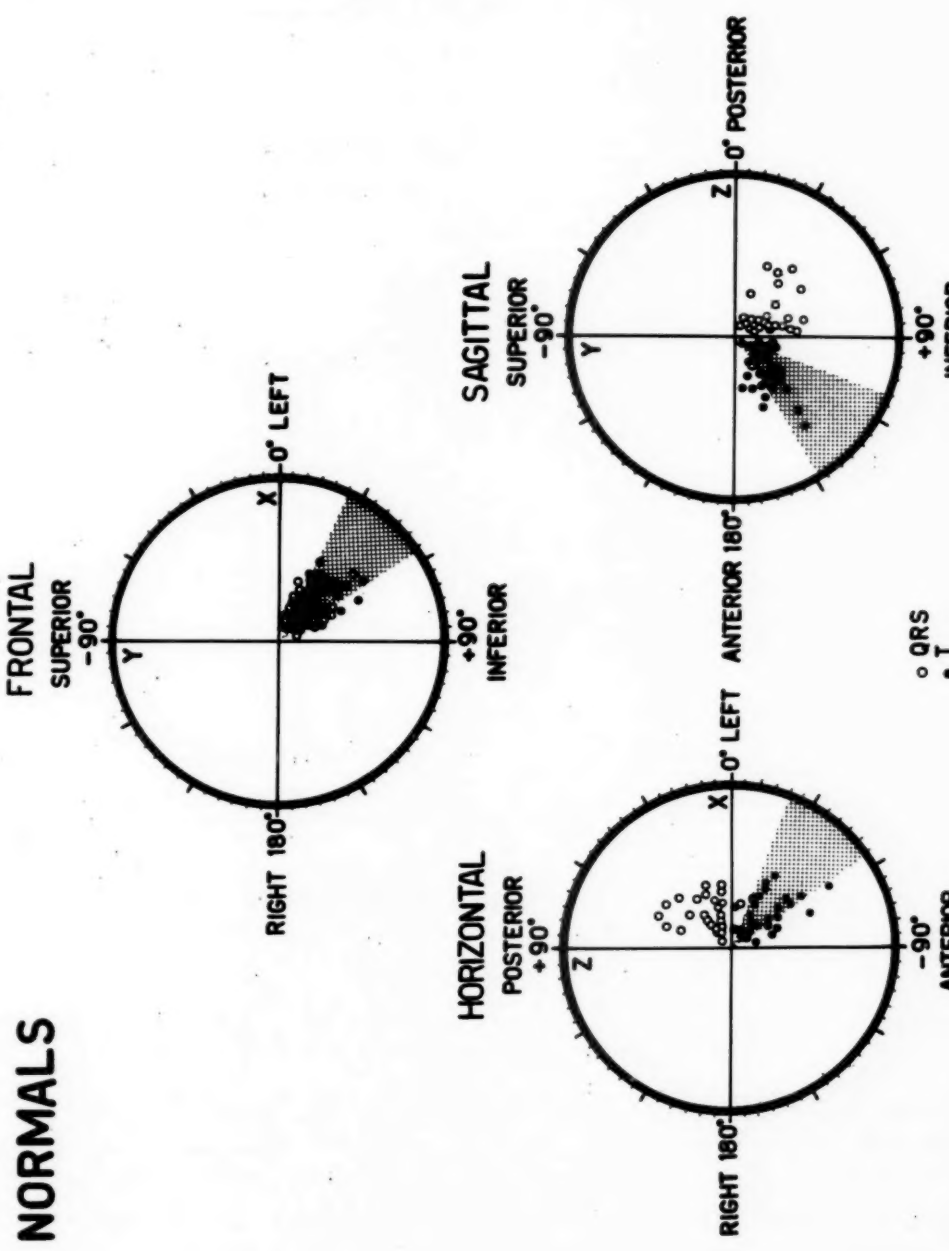

Fig. 1.—Direction and magnitude of QRS and T-area vectors on horizontal, frontal, and sagittal planes in normal subjects. QRS vectors, open circles; T vectors, solid circles. Cross-hatched areas represent standard deviations of T direction in each plane.

$r = 0.642$, the t-value for r ($t = 4.10$) corresponding to $p < 0.01$. This relationship can be expressed by a regression equation $\hat{T}_A = 10.6 + 0.785\ QRS_A$ (see Fig. 3,*A*).

A statistically significant correlation has been found also between spatial T-area magnitudes and the dA° angles, which can be expressed by a regression equation $\hat{T}_A = 10.9 + 0.529$ dA° (see Fig. 4,*A*); $r = 0.705$ and the t-value for r ($t = 4.85$) corresponds to $p < 0.01$.

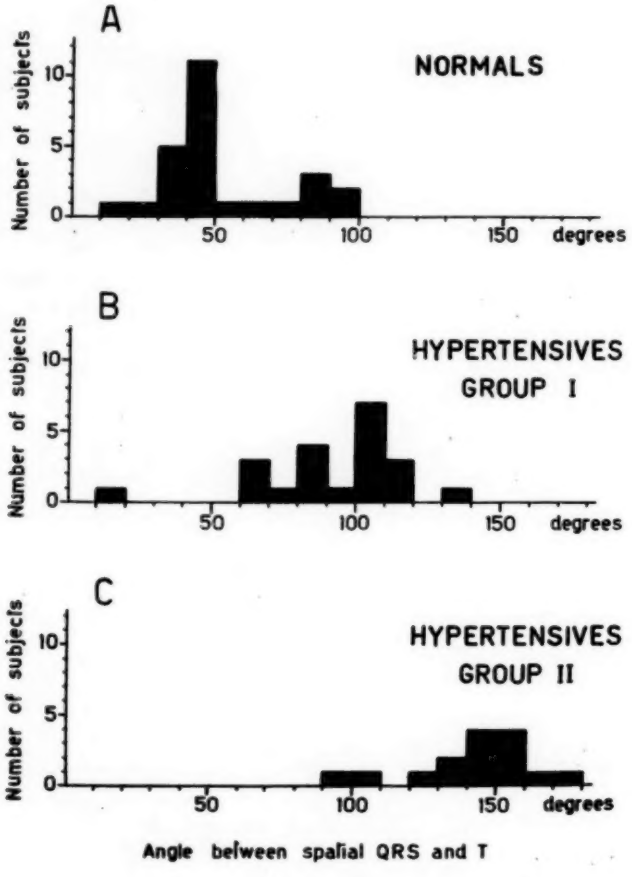

Fig. 2.—Frequency distribution of angles (dA°) between spatial QRS and T vectors in normal subjects (*A*), and in hypertensive patients (*B*: Group I; *C*: Group II).

The dependence of spatial T-area magnitude on both spatial QRS area and dA° has been studied: the multiple regression equation has been found to be $\hat{T}_A = 4.8 + 0.408\ QRS_A + 0.374$ dA°, the t-test of significance for the two regression coefficients being 1.94 and 2.91, respectively ($p = 0.1$ and 0.01). The multiple regression coefficient ($R = 0.752$) is greater than either of the partial regression coefficients ($r_{y1} = 0.642$ and $r_{y2} = 0.705$), and the multiple regression as an entity has been found to be highly significant ($p < 0.01$) both by an analysis of variance ($F = 15.01$, with 2 and 23 degrees of freedom) and by simply checking an adequate table (see Reference 27, Table 13.6).

Hypertensive Patients: Group I.—This group includes all patients with no signs of abnormal repolarization on conventional electrocardiographic tracings,

The observations obtained from this group are schematically presented in Fig. 5 and summarized in Table I.

The direction of the QRS- and T-area vectors has not fundamentally changed from that characteristic of normal subjects, the QRS vector being directed leftward, downward and posteriorly, the T vector being directed leftward, downward and anteriorly. However, closer observation shows that QRS vectors are placed

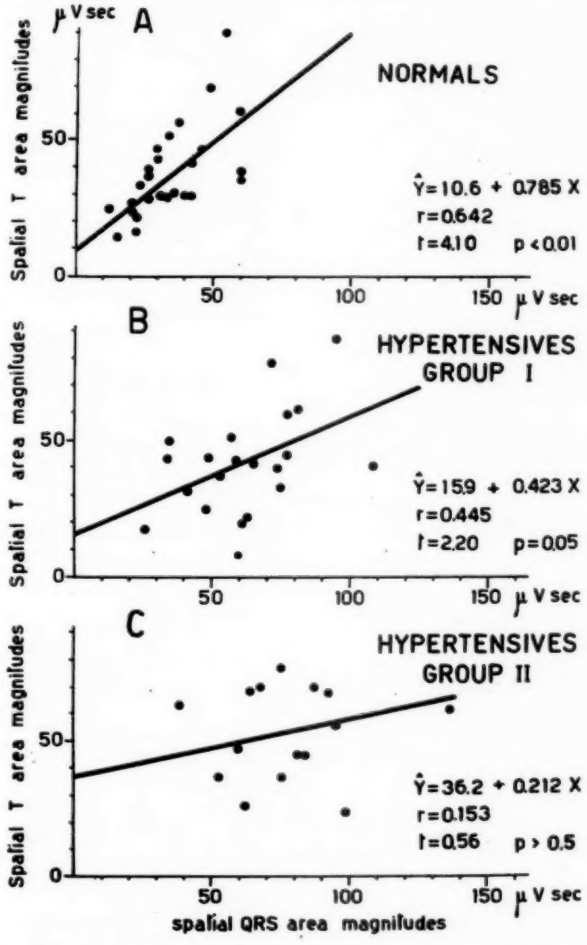

Fig. 3.—Relationship between spatial depolarization and repolarization vectors in normal and hypertensive subjects. The highly significant correlation ($p < 0.01$), which is present in normal subjects (*A*), is definitely less significant ($p = 0.05$) in the first group of hypertensive patients (*B*), and is completely lost in the second group of patients (*C*).

in a slightly more horizontal position and are somewhat more variable in direction. Likewise, T vectors are directed slightly more anteriorly and are more variable than in the normal population. As a result, the dA° angles are definitely increased, averaging 91 degrees ($s = 27$): their frequency distribution shows a peak between 80 and 120 degrees (Fig. 2,*B*). Statistical tests show that this increase is significant ($F = 29.91$, with 1 and 45 degrees of freedom; $p<0.01$).

QRS-area vector magnitudes are clearly augmented in each plane: accordingly, mean calculated spatial QRS-area magnitude measures 62.3 μVsec

(s = 20.4). T-area vector magnitudes are also increased but in a somewhat lesser degree than QRS areas, the mean spatial T-area magnitude measuring 42.4 μVsec (s = 19.3).

Spatial ventricular gradient magnitudes, averaging 75.1 μVsec (s = 27.4), are definitely augmented as compared to normal values (F = 12.8, with 1 and 45 degrees of freedom; $p < 0.01$), whereas the angles circumscribed by the QRS and ventricular gradient vectors are not significantly altered.

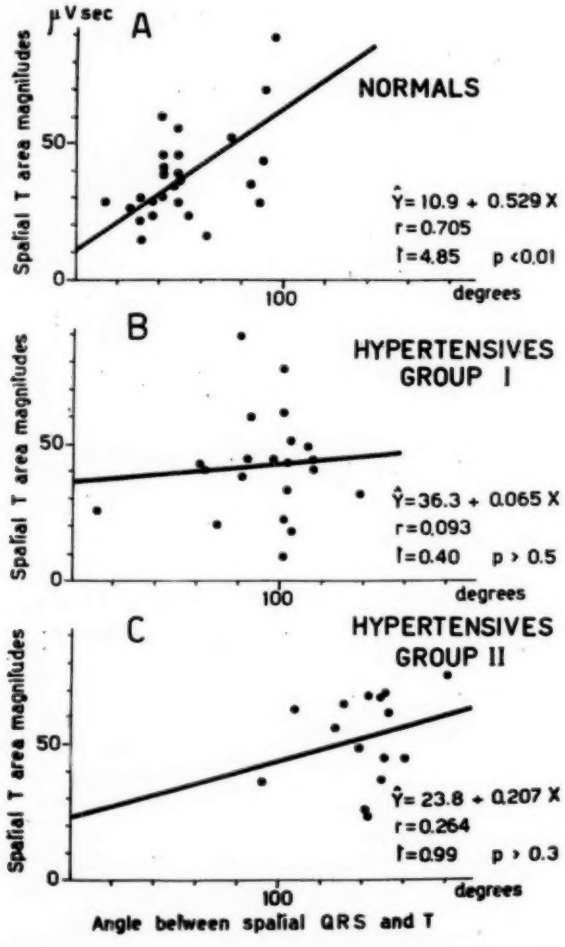

Fig. 4.—Relationship of the angle between spatial depolarization and repolarization vectors with repolarization vector magnitude, in normal and hypertensive subjects. The highly significant correlation ($p < 0.01$) which is present in normal subjects (*A*) is entirely lost in both groups of hypertensive patients (*B*, *C*).

The correlation between spatial QRS and T areas was still preserved in this group of patients, although less well than in normal subjects, r being 0.445 and the t-value for r (t = 2.20) corresponding to p = 0.05. The relationship between the vectors was found to be expressed by a regression equation $\hat{T}_A = 15.9 + 0.423\ QRS_A$, as though T size were less dependent on QRS magnitude than in normal subjects. Although this difference between normal subjects and the first group of hypertensive patients fell short of statistical significance (F = 3.68, with 1 and

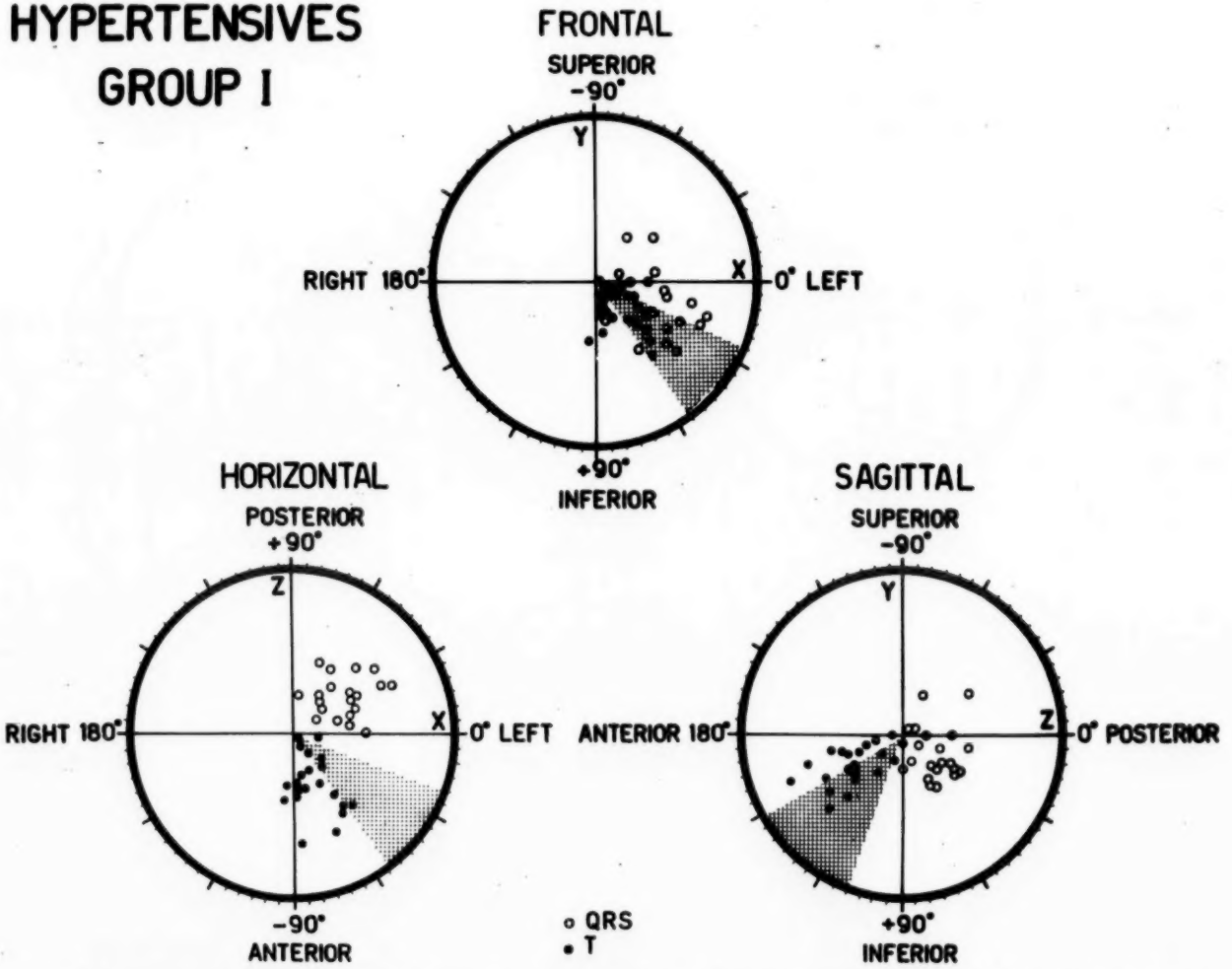

Fig. 5.—Direction and magnitude of QRS- and T-area vectors on horizontal, frontal, and sagittal planes, in the first group of hypertensive patients. QRS vectors, open circles; T vectors, solid circles. To emphasize deviations from normal values, cross-hatched areas show standard deviations of T-vector direction in normal subjects.

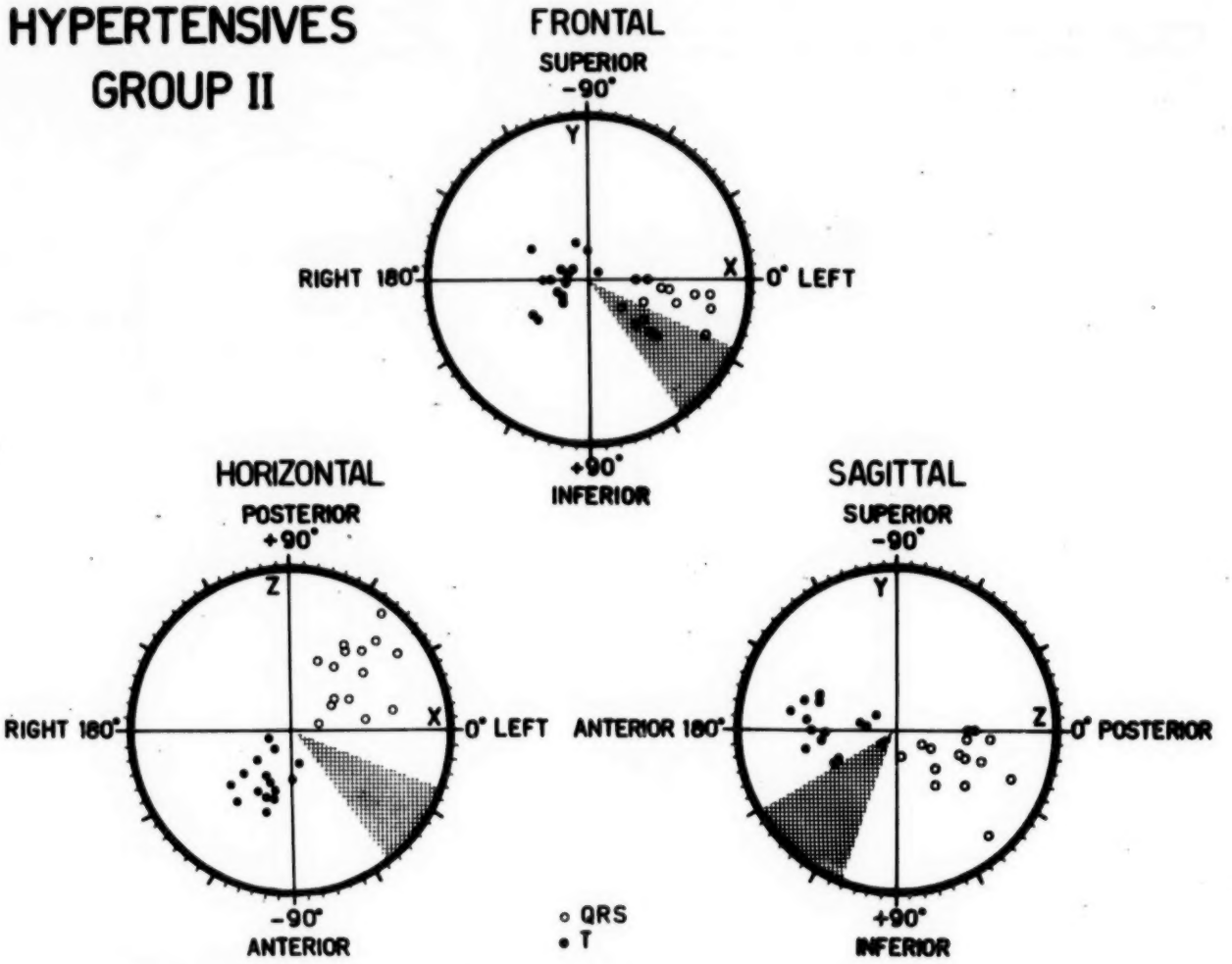

Fig. 6.—Direction and magnitude of QRS- and T-area vectors on horizontal, frontal, and sagittal planes, in the second group of hypertensive patients. QRS vectors, open circles; T vectors, solid circles. To emphasize deviations from normal values, cross-hatched areas show standard deviations of T-vector direction in normal subjects.

44 degrees of freedom), a highly significant difference in the behavior of the two populations was found when spatial T-area magnitudes were studied versus the angles dA°: the definite correlation present in normal subjects ($r = 0.705$, $t = 4.85$, $p < 0.01$) is entirely lost even in the hypertensive patients of the first group ($r = 0.03$, $t = 0.40$, $p > 0.5$), as though T magnitude were not dependent any longer on the angle delimited by depolarization and repolarization vectors. Consequently, no multiple regression of T magnitudes on QRS magnitudes and dA° angles could be calculated in hypertensive patients.

Hypertensive Patients: Group II.—It has already been pointed out that this group includes all patients with signs of abnormal repolarization on conventional electrocardiographic tracings. The observations obtained from this group are presented in Fig. 6 and summarized in Table I.

The normal direction of the QRS- and T-area vectors, which was roughly preserved in the first group of our patients, appears completely upset in these severely hypertensive patients. Whereas the QRS vector is still directed leftward, downward and posteriorly, the T vector has changed from its normal leftward, downward and forward direction to a new position in space, being directed rightward, upward and forward. As a consequence, the dA° angles have exceedingly increased in magnitude, even when compared to the values displayed by the first group of hypertensive patients. Mean value measures 141 degrees ($s = 21$), the frequency distribution showing a peak between 130 and 160 degrees (see Fig. 2,*C*). Statistical tests show that this increase is highly significant ($F = 68.85$, with 2 and 59 degrees of freedom; $p < 0.01$).

QRS-vector magnitudes show further augmentation on each plane: accordingly, mean calculated spatial QRS-area magnitude measures 78.1 μVsec ($s = 23.1$). Slight increases in T-area vector magnitudes are also observed, mean spatial T-area magnitude measuring 52.7 μVsec ($s = 16.6$).

Spatial ventricular gradients average 51.8 μVsec ($s = 30.1$) in magnitude, the mean angle delimited by the QRS and gradient vectors being 37 degrees ($s = 24$).

Interestingly enough, when the relationship between spatial QRS- and T-area magnitudes is studied in hypertensive patients with electrocardiographic evidence of overload, it is found that the correlation which was present in normal subjects and was still preserved in the hypertensive patients of Group I is now completely lost; r is only 0.153, and a t-value of 0.56 corresponds to $p > 0.5$. Needless to say, also the normal correlation between dA° and T magnitude, which had already disappeared in the hypertensive patients of Group I, is no longer present in these severe cases ($r = 0.264$, $t = 0.99$, $p > 0.3$).

DISCUSSION

Applying corrected orthogonal leads to a study of spatial electrocardiographic patterns in normal and in hypertensive subjects has enabled us to confirm and better estimate several observations which were already classic in conventional electrocardiography. Among these confirmations of older findings are the augmentation of QRS-vector magnitude and its change to a more horizontal direction

early in arterial hypertension.[29,30] However, the more accurate quantitative techniques employed in our study show that, when considered in space, deviation of the QRS vector is far less conspicuous even in severely hypertensive patients than it may appear to be by conventional twelve-lead electrocardiography. Also, the change of the T-wave vector to a more frontal direction in hypertensive patients with moderate heart involvement, and its shift to an upward and rightward direction in overloaded patients are not entirely new, since these changes could be surmised from the increased positivity of the T wave in Lead V_2 and its flattening in left ventricular precordial leads.

Likewise, widening of the spatial angle between QRS and T vectors had already been suggested as occurring in hypertensive patients with "left ventricular hypertrophy,"[24,31] but lack of accurate means of quantitative measurement in space did not enable agreement on whether it would have some pathologic meaning or would simply result from the increase in QRS-vector magnitude as a compensatory mechanism to avoid changes of the ventricular gradient.[24] This is not an idle question, since widening of dA° is the only change in the repolarization process which can be evidenced in hypertensive patients without signs of overload, and it is of obvious importance to establish whether repolarization is either altered or unaltered in these hypertensive patients. Understanding of this problem has been helped by the study of the correlations existing between QRS- and T-vector magnitudes, and between dA° and T magnitude in normal subjects. Indeed, we have been able to confirm the strict correlation which had been shown to exist between QRS- and T-vector magnitudes.[23] The correlation coefficient obtained from our spatial observations ($r = 0.642$) compares favorably with that derived by Simonson and associates[23] from less accurate spatial measurements ($r = 0.586$), and supports the accuracy of Frank's method. Even more striking is the correlation which we have demonstrated as existing between T-wave magnitude and dA° ($r = 0.705$). The multiple correlation between dA°, QRS and T magnitudes, and the consequent multiple regression equation, are a final demonstration of the type of relationship existing between these phenomena. When the magnitude of the repolarization vector is considered to be dependent both on the depolarization vector magnitude and on the spatial angle dA°, the correlation coefficient ($R = 0.752$) is definitely greater, as though T magnitude might be better calculated from both QRS magnitude and dA°.

The existence of a numerical relationship between depolarization and repolarization phenomena, being indispensable for the ventricular gradient concept,[23] would seem to strengthen the present definition of this concept and support the hypothesis that widening of dA° in hypertensive patients with "left ventricular hypertrophy" is a physiologic mechanism to keep gradient magnitude and angle at constant values.[24] However, the sign of the numerical relationship we have calculated to exist is not such as to result in a ventricular gradient that is constant either in magnitude or direction. Furthermore, in those very patients in whom, according to Gardberg and Rosen's contention,[24] changes in T magnitude and in the angle dA° should be strictly dependent on each other, and on QRS magnitude, any such multiple relationship is definitely lost. Therefore it does not appear unsafe to surmise that widening of dA° in hypertensive patients

is an early sign of alteration in the repolarization process, a conclusion which is supported by the further widening of the spatial angle in severely overloaded hypertensive patients.

The numerical relationship which we have calculated to occur between dA°, QRS and T magnitudes in normal subjects has also obvious implication for the ventricular gradient concept, which goes further than we are prone to do on the basis of our present evidence. It might be amiss to try now to appraise the functional meaning of the increased gradient magnitude which we have observed in hypertensive patients with moderate heart involvement, and the return to approximately normal values in severely overloaded patients. It does appear that several concepts which are now current in electrocardiography, and which have been derived from frontal plane measurements only or with uncorrected spatial leads, need to be evaluated anew with the help of the accurate spatial systems of leading presently available. It is self-evident that any concept which is derived from quantitative implications, useful as it might have appeared in clinical electrocardiography, can be assessed only on the basis of correct quantitative measurement.

SUMMARY

1. A study of the spatial electrocardiographic patterns has been performed in patients with arterial hypertension, using Frank's corrected orthogonal system, and the results obtained have been compared to the patterns characteristic of normal subjects.

2. Spatial QRS- and T-vector magnitude and direction, and the angle between the two (dA°) have been measured preliminarily in normal subjects, and a definite correlation has been found to exist between spatial QRS and T magnitudes, and between dA° and T magnitude. A multiple regression equation showing dependence of T magnitude on both QRS magnitude and dA° has been calculated and the relation found highly significant.

3. In hypertensive patients with no signs of altered repolarization on conventional electrocardiographic leads the most striking feature has been found to be a widening of dA° and an absent correlation between dA° and T magnitude. These phenomena are paralleled by a definite increase in ventricular gradient magnitude. Widening of dA° has therefore been assumed to represent an early sign of altered repolarization which may not be evident from qualitative evaluation of conventional leads.

4. In hypertensive patients with electrocardiographic signs of overload the direction of the T vector has been found to be completely upset, so that a further widening of dA° results. Any correlation between QRS, T, and dA° magnitude is completely lost.

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Atrial Flutter With 1:1 A-V Conduction Associated With Pulmonary Embolism in the Aged

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Atrial flutter with 1:1 atrioventricular conduction is considered to be a rare clinical entity.[1,2] Finkelstein, Gold, and Bellet, in 1956, described 6 patients with this arrhythmia and were able to discover 40 other cases which had been published previously.[1] They found no patients over the age of 60, a finding which might be explained by the development of degenerative changes in the A-V nodes of elderly subjects and a resulting decrease in the ability of such nodes to conduct rapid atrial impulses. It is the purpose of this report to describe 2 patients, aged 65 and 70, in whom atrial flutter with 1:1 A-V conduction was present. It is of further interest that the arrhythmia was associated in each patient with the occurrence of pulmonary emboli.

CASE REPORTS

CASE 1.—G. T., a 65-year-old Negro man, was admitted to the Philadelphia General Hospital, on Dec. 29, 1958. Ten days prior to admission he was reported to have had an episode of chest pain which was followed 2 days later by swelling of his left leg. Further history was unobtainable because of the patient's extreme disorientation. On physical examination he had a rectal temperature of 100°F., a respiratory rate of 35 per minute, a blood pressure of 150/100 mm. Hg, and a heart rate of 240 per minute. The neck veins were moderately distended when the patient was in the sitting position, and inspiratory wheezes were heard throughout both lungs. No cardiac murmurs were detected. His left leg was warm, red, swollen, and tender. An electrocardiogram (Fig. 1,*A*) showed atrial flutter with 1:1 A-V conduction, ventricular aberration, and occasional short periods of atrial flutter with 2:1 A-V conduction. Carotid sinus pressure had no effect on the cardiac rate or rhythm.

During the first 8 hours of hospitalization, 2 mg. of Cedilanid were given intravenously in divided doses of 0.2, 0.8, 0.4, and 0.6 mg. At the end of this time the electrocardiogram (Fig. 1,*C*) showed an atrial flutter with 2:1 A-V conduction and a normal intraventricular conduction time. During the next 19 hours, an additional 2.4 mg. of Cedilanid were administered intravenously. The rhythm (Fig. 1,*D*) changed to a flutter-fibrillation with a ventricular rate of 90 per minute. Cedilanid was then withheld for 12 hours, and the patient's rhythm reverted to an atrial flutter with 2:1 A-V conduction (Fig. 1,*E*). In an effort to achieve maximal slowing of the cardiac rate or to convert the abnormal rhythm to a normal one, 1.0 mg. of Cedilanid, followed in 1 hour by 0.6 mg. of Cedilanid were then given intravenously. One hour after the last dose of Cedilanid the

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atrial rhythm had changed to a flutter-fibrillation with a ventricular rate of 70 to 80 beats per minute (Fig. 1,*F*). No extrasystoles were noted. One-half hour later, while the patient was being rolled over to remove a bedpan, he sat up, gasped, and died. During a period of 42 hours, he had received a total of 6.0 mg. of Cedilanid. Heparin in doses of 150 mg. was injected subcutaneously into the supragluteal fat pad every 12 hours during the same period.

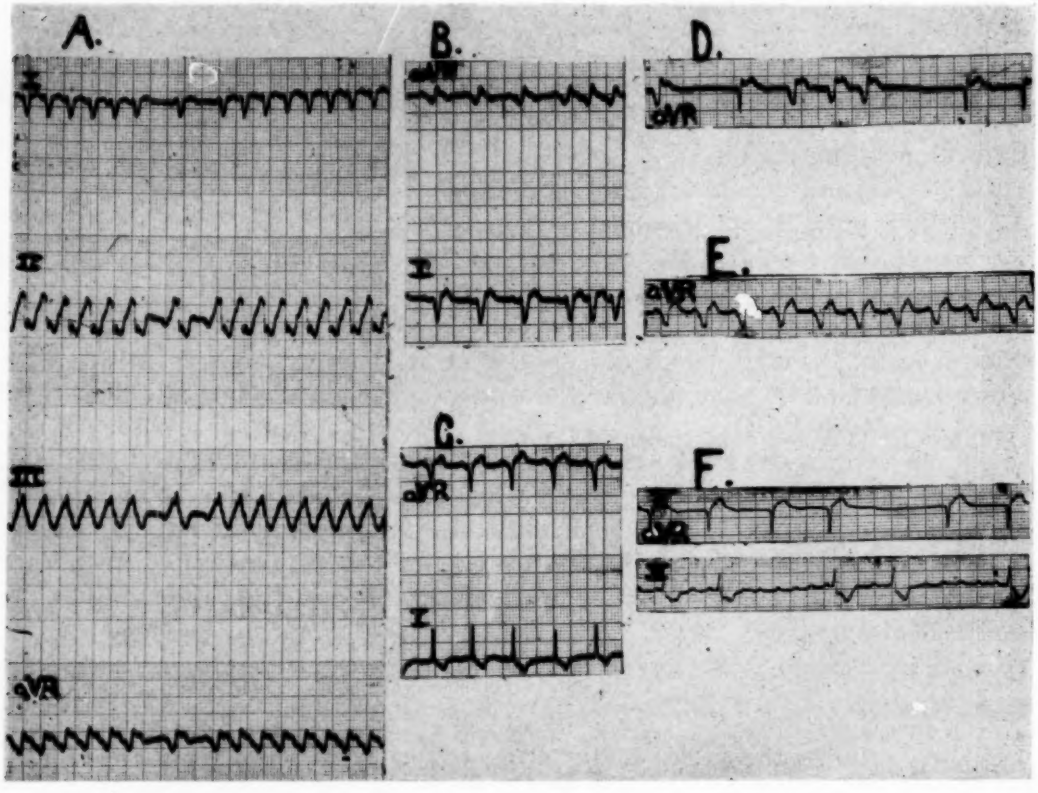

Fig. 1.—Patient G. T. *A*, Pretreatment electrocardiogram showing atrial flutter with 1:1 A-V conduction and ventricular aberration. A brief period of 2:1 A-V conduction is also shown. (Simultaneous recording of Leads I, II, III, and aVR.) *B*, After the administration of 1.4 mg. of Cedilanid in the first 6 hours of therapy, the rhythm had been converted to atrial flutter with 2:1 A-V conduction. The ventricular aberration persisted. (Simultaneous recording of Leads aVR and I.) *C*, After the administration of 2.0 mg. of Cedilanid in the first 8 hours of therapy, the rhythm was atrial flutter with 2:1 A-V conduction and normal intraventricular conduction. (Simultaneous recording of Leads aVR and I.) *D*, Twenty-seven hours after the start of therapy, the patient had received 4.4 mg. of Cedilanid. The ventricular rate had slowed and the atrial rhythm had become flutter-fibrillation (Lead aVR). *E*, During the next 12 hours, additional Cedilanid was withheld, and the rhythm reverted to atrial flutter with 2:1 A-V conduction (Lead aVR). *F*, Two and one-half hours after *E*, an additional 1.6 mg. of Cedilanid had been administered. The patient died one-half hour later. (Leads aVR and II, the latter showing the atrial activity.)

Autopsy revealed a carcinoma of the prostate, with local extension to the seminal vesicles and bladder. Thrombi were found in the left iliac and left femoral veins. The heart weighed 440 grams. The right ventricle was dilated and hypertrophied. A mural thrombus was present in the dilated right atrial appendage. All the heart valves were normal. The aorta and coronary arteries showed only minimal atherosclerotic changes. Multiple emboli were present in the pulmonary vessels, producing extensive infarction of the right and left lower lobes. Some of the emboli showed organization, whereas others appeared to be of more recent occurrence.

CASE 2.—H. H., a 70-year-old Negro man, was admitted in a comatose state to the Philadelphia General Hospital, on Oct. 13, 1954. On physical examination the patient had a temperature

of 100.5°F., a systolic blood pressure of 120 mm. Hg (no diastolic pressure was recorded), a heart rate of 230 per minute, and a respiratory rate of 40 per minute. A left hemiplegia was present. No cardiac murmurs were heard. The lungs were clear to auscultation and percussion. An electrocardiogram (Fig. 2,*A*) revealed the presence of atrial flutter with 1:1 A-V conduction and ventricular aberration. Neither the rate nor the rhythm was altered by carotid sinus pressure. After a single intravenous dose of 0.8 mg. of Cedilanid the rhythm was changed to an atrial flutter with 2:1 A-V conduction and normal intraventricular conduction (Fig. 2,*B*). With the slowing of the ventricular rate, a Grade 2 systolic murmur and a protodiastolic gallop sound became audible at the apex of the heart. The patient's blood pressure at this time was 120/70 mm. Hg.

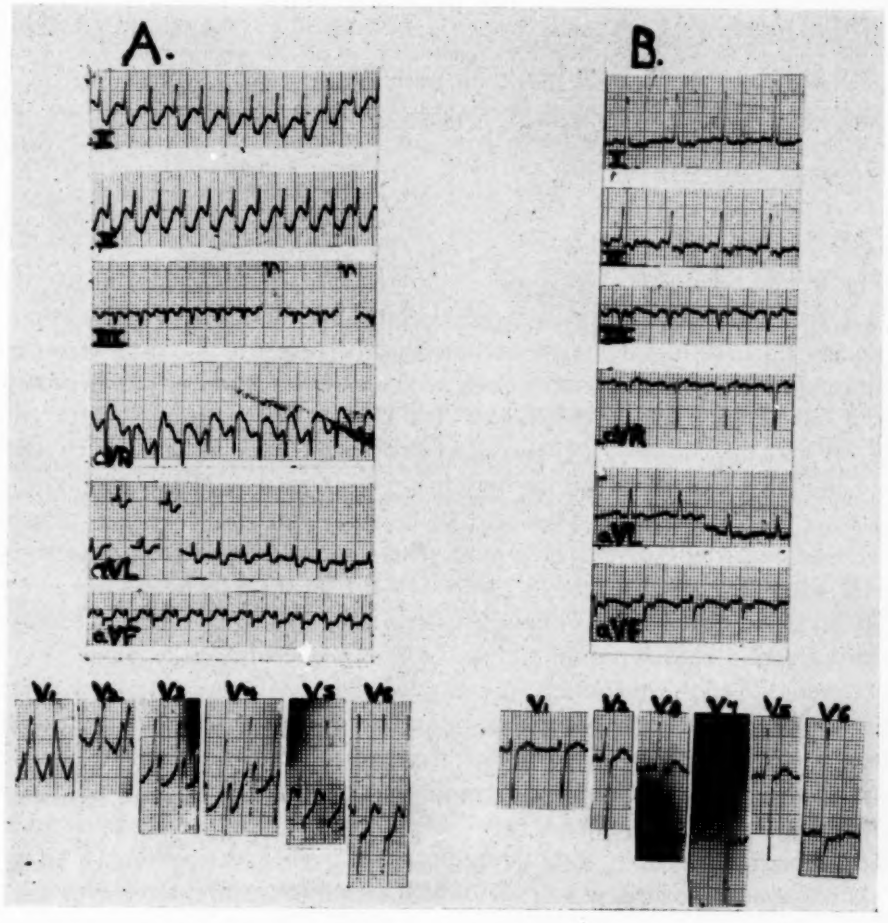

Fig. 2.—Patient H. H. *A*, Pretreatment electrocardiogram showing the presence of atrial flutter with 1:1 A-V conduction. *B*, After the administration of 0.8 mg. of Cedilanid, the rhythm had been converted to atrial flutter with 2:1 A-V conduction.

On Oct. 16, 1954, the patient's temperature rose to 103°F., and râles were heard at both lung bases. His condition gradually worsened, and he died on October 26, never having regained consciousness.

From the second to the sixth days of hospitalization the patient received 0.3 Gm. of digitalis leaf daily. During the remainder of his illness he was given 0.1 Gm. of digitalis leaf per day. On the seventh hospital day, 0.2 Gm. of quinidine sulfate was given every 2 hours for five doses. For the ensuing 3 days, quinidine sulfate was administered in a similar manner, increasing from 0.3 Gm. per dose on the eighth and ninth days to 0.4 Gm. per dose on the tenth day. Neither

quinidine nor digitalis in the doses used were associated with conversion of the abnormal rhythm to a normal one. It is interesting to note that on one occasion, during the administration of quinidine sulfate in the presence of atrial flutter with 2:1 A-V conduction, the atrial rate slowed to 200, and a 1:1 A-V conduction was re-established. Further doses of Cedilanid led to the return of a 2:1 A-V block.

Laboratory data on admission included a hemoglobin of 12.6 Gm. per cent, a white blood cell count of 12.4 thousand per cubic millimeter, and a blood urea nitrogen of 20 mg. per cent. Examination of the cerebrospinal fluid revealed a protein content of 160 mg. per cent, 1,026 red blood cells per cubic millimeter, and 14 white blood cells per cubic millimeter.

An autopsy performed on Oct. 26, 1954, disclosed atherosclerosis of the aorta and coronary arteries. The heart weighed 420 grams. The atria were dilated and the ventricles hypertrophied. All the valves were normal except for the mitral valve, which was slightly thickened. No thrombi were noted in the cardiac chambers. Examination of the lungs showed emphysema, bronchopneumonia, and thrombi in the branches of the pulmonary arteries. Infarcts were noted in the spleen and kidneys, and, in addition, the latter showed the changes of arteriolar nephrosclerosis. The cerebral vessels were atherosclerotic, and there were old and new areas of encephalomalacia.

DISCUSSION

The following electrocardiographic criteria[1] for the diagnosis of atrial flutter with 1:1 A-V conduction were satisfied by the patients described in this report: (1) the presence of atrial waves occurring at a rate of 225 to 315 per minute, accompanied by a ventricular response to each atrial impulse; (2) demonstration of atrial flutter with higher degrees of A-V block either before or after the onset of the 1:1 arrhythmia; and (3) response to treatment of an ectopic rhythm with a rapid ventricular rate by either increasing degrees of A-V block or atrial fibrillation.

To our knowledge, the cases presented here represent the oldest reported patients with this arrhythmia in the medical literature. The occurrence of this arrhythmia in these patients demonstrates that in spite of advanced age, rapid transmission of atrial impulses across the A-V node may take place.

Accepted etiological factors in the production of atrial flutter with 1:1 A-V conduction include serious myocardial damage; increased sympathetic tone, such as occurs during exertion, emotional strain, and the induction of anesthesia[1]; quinidine, which when used in the treatment of atrial flutter with partial degrees of A-V block may slow the atrial rate sufficiently to allow the ventricle to respond to each atrial impulse[3,4]; and atropine when given intravenously to patients with rheumatic heart disease and atrial fibrillation or atrial flutter with 2:1 block.[5]

Although pulmonary embolism may frequently precipitate atrial arrhythmias,[6-8] it has not to our knowledge been reported to cause atrial flutter with 1:1 A-V conduction. In Patient G. T. the clinical history seemed to indicate that the pulmonary embolism was the stimulus for the arrhythmia, whereas in Patient H. H. the finding at autopsy of thrombi in the pulmonary arteries was suggestive of a causal relationship. It seems less likely that emoblism occurred in either patient as a result of atrial flutter, in view of Hejtmancik's finding of a decreased incidence of emboli in patients with this arrhythmia.[9]

Sudden pulmonary arterial obstruction hinders the outflow of blood from the right ventricle and produces distention of the right ventricle, right atrium, and peripheral veins.[10] Stretch of the atrium has been shown by Scherf[11] and

Prinzmetal[12] to produce atrial fibrillation in the experimental animal. It is conceivable that the distention of the right atrium, which may occur with pulmonary embolism, could be an important factor in the precipitation of other atrial arrhythmias. Experimental evidence[10] suggests that sympathetic impulses may be active following pulmonary embolization, and that, in addition, there may be cardiac anoxia. Any or all of these factors may have been involved in the production of the arrhythmias reported here.

SUMMARY

Atrial flutter with 1:1 A-V conduction occurring in 2 patients over 60 years of age is reported. The etiological significance of pulmonary embolism is discussed.

The authors wish to express their appreciation to Miss Roberta Cope and to Mrs. Anita Spivack for their assistance in preparing the manuscript.

ADDENDUM

Since the time this paper was submitted for publication, the authors have observed a 67-year-old Negro man in whom atrial flutter with 1:1 A-V conduction was associated with pulmonary embolism. On admission, the patient's heart rate was 240 per minute and his blood pressure was 100/70 mm. Hg. An electrocardiogram showed atrial flutter with 1:1 A-V conduction and ventricular aberration of a right bundle branch block type. One hour and forty minutes after the administration of 0.8 mg. of Cedilanid, the rhythm changed to atrial fibrillation. A chest x-ray obtained shortly after admission showed a pleuropneumonic process in the left lower lung field. Aspiration of a small pleural effusion in this area, two days later, revealed xanthochromic fluid with many red blood cells. One month following the date of admission, he was discharged on maintenance doses of digitalis, but died two months after discharge. Autopsy revealed a heart that weighed 690 grams, with an intramural thrombus in the right atrium. All the chambers of the heart were enlarged. Multiple small emboli were found throughout the lungs. Pathologic diagnosis of the myocardial disease was primary amyloidosis.

The finding by Rytand and associates[13] of atrial flutter with slow atrial rates in association with right atrial enlargement seems to be supported by the cases reported above.

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Circulatory Reactions of Normotensive and Hypertensive Subjects and of the Children of Normal and Hypertensive Parents

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There is substantial agreement that high blood pressure is a familial trait.[1-5] The careful studies of Miall and Oldham[1] and of Hamilton, Pickering, Roberts and Sowry[2] indicate a higher average blood pressure among the relatives of hypertensive than of normotensive subjects. Hines, McIlhaney, and Gage[5] described the occurrence of hypertension in 8 pairs of identical twins, whereas in 3 pairs of fraternal twins the disease occurred in only one member. Despite these studies, few efforts have been made to identify the earliest age at which the blood pressure of the children of hypertensive parents may be expected to deviate from the values observed in the offspring of normal parents. Ayman,[3] however, found a blood pressure in excess of 140/80 mm. Hg in 29 per cent of the progeny aged 14-39 of hypertensive parents, as compared to a 3 per cent incidence of similar blood pressure elevation in the offspring of normotensive parents.

Although the familial aspects of hypertension have been agreed upon, the evidence is less consistent that exposure to various forms of stress may unduly elevate the blood pressure of prehypertensive subjects. Hines[6] reported subsequent hypertension in 9 per cent of 84 normal reactors and in 54 per cent of 105 hyperreactors to an ice-water immersion test. On the other hand, Harlan[7] and Armstrong and Rafferty[8] could not confirm this finding. Hines also found an excessive rise in blood pressure to the cold pressor stimulus in hypertensive patients, when compared to normal control subjects.[9,10] Other authors have found less consistent differences in the cold pressor responsiveness of the normal and the hypertensive subject[11,12] or have observed considerable inconsistency in the response of the same individual to repeated testing.[7,13] Other stimuli, such as breath-holding,[14] exercise,[15] and change in posture,[16] have also been tried in a further attempt to distinguish a normal from a hypertensive response.

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The major portion of this work is described in greater detail in a dissertation presented by Dr. Remington in partial fulfillment of the degree of Doctor of Philosophy in Public Health Statistics at the University of Michigan. A full account of the statistical methods and conclusions will be published elsewhere by the senior author.

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Since there seemed to be doubt that any individual test of vascular reactivity could distinguish the overt or potentially hypertensive subject from the normal one, the present study was designed to examine the effect of four simple tests on the blood pressure of subjects with established and labile hypertension and of young individuals with and without a proved family history of the disease. In the course of such a study on blood pressure, it was also intended to learn whether the children of hypertensive parents exhibited at the teen-age level a higher blood pressure than did control subjects of similar age and sex.

METHODS

Selection of Subjects.—Tests were performed on 50 children aged 8 to 18, one of whose parents was attending the hypertension clinic of the University of Michigan Hospital. Each individual was then matched according to age and sex with a child who was selected from a list of students attending the University Elementary or High School,* and an identical series of tests was then performed on the control subject in the hypertension clinic. Every effort was made to perform the tests in an identical manner, and except for the fact that the examiner usually knew to which series the subject belonged and that the children of hypertensive parents traveled farther to reach the clinic, no important difference between the two series of tests was recognized. Whereas in the original survey, only patients of the white race were tested, it was later possible to perform a similar series of tests on Negro school children in the city of Nassau,† Bahamas, an area with a reported high rate of hypertension in the adult population.[17] In the ensuing discussion, Group I will refer to the children of the normotensive parents, Group II the offspring of hypertensive subjects, and Group III will be used to designate the Bahamian school children.

For the purpose of comparing the response to the series of tests of adult subjects with and without hypertension, three groups were studied: 10 normotensive laboratory workers (N), 10 patients with labile hypertension (L), and 9 subjects with an apparently established form of

TABLE I. CHARACTERISTICS OF THE STUDY GROUPS

GROUPS	SEX		MEAN ARM GIRTH (INCHES)	MEAN AGE (YR.)	MEAN FINAL RECUMBENT READING	
	M	F			BLOOD PRESSURE (MM. Hg) S*/D*	PULSE RATE
Normotensives	6	4	**	32.3	107/63	74
Labile Hypertensives	6	4	**	31.8	135/84	85
Established Hypertensives	5	4	**	42.8	191/121	85
Children of Normotensive Parents	25	25	8.8	12.7	104/59	88
Children of Hypertensive Parents	25	25	8.7	12.6	108/60	80
Children of Bahamian Parents	15	16	8.6	13.8	117/65	80

*S = Systolic. D = Diastolic.
**Not recorded.

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†We wish to express our gratitude to Dr. Freda Bonner, school physician, and to Dr. E. H. Murcott, Chief Medical Officer of the Bahama's Government Medical Service for their very kind cooperation in providing the facilities and assisting us in obtaining the subjects for these tests.

the disease (H). The patients with labile hypertension had records of previous casual blood pressure readings in excess of 152/90 mm. Hg (mean = 177/91), but they were in the near-normotensive range when the tests were performed. The subjects with established hypertension had shown repeated and consistent elevation of the blood pressure above 168/98 mm. Hg (mean resting level = 191/121). No patients were undergoing antihypertensive treatment at the time of testing, although one had had an unsuccessful splanchnicectomy. In Table I the characteristics of the various study groups are presented.

DETAILS OF TEST PROCEDURES*

The studies were carried out in a quiet examining room at least 1 hour postprandially. Conversation was kept to a minimum, but an easy, comfortable relationship was the goal in each case. Explanation of the procedure to be followed preceded each test, after which a 3-minute rest period elapsed. Readings were taken in most instances by the authors, and after the rest period and postural test the order of administration of the cold pressor, breath-holding, and exercise tests was varied at random. The tests were applied by the same examiner and in the same order to each of the paired subjects in Groups I and II. Blood pressures were taken from the left arm, and pulse rates at the right wrist. A standard aneroid sphygmomanometer, which was frequently calibrated against a mercury manometer, was used. The standard child-size cuff (3-¾ inches) was used on two children in Group I and on three children in Group II. The decision to use the smaller cuff was made on the basis of arm length—the cuff of width closest to two thirds of the length of the arm being chosen. The complete disappearance of sounds (Phase V) served as the criterion for diastolic blood pressure.

Rest Period.—Upon arriving for the series of tests, the subject entered an examining room where, while he was standing, his blood pressure and pulse rate were taken immediately. He then lay on the bed while the blood pressure and pulse rate were again determined. Readings† were then taken after 5, 10, 15, and 20 minutes' rest; between determinations the subject was left alone in the room.

Postural Test.—After the 20-minute resting reading and a brief verbal indication that the observer would remain in the room, three recumbent readings were taken at 1-minute intervals, the last being designated as the *final recumbent blood pressure.* The subject was asked to stand beside the bed, and a reading was taken immediately and every minute thereafter for 3 minutes.

Cold Pressor Test.—Following verbal instructions, a reading was taken with the subject recumbent and again after 3 minutes. The right hand was then immersed in the ice water to a point approximately 1 inch above the wrist line, and a blood pressure reading was taken after 30 seconds and after 60 seconds of immersion. The hand was withdrawn from the water and a pulse rate was taken. Measurements were made thereafter every minute for 3 minutes. The test procedure resembled that described by Hines,[16] except for the abbreviated rest period.

Breath-Holding Test.—The subject was seated in a comfortable chair and given verbal instructions, including a warning not to strain, in order to avoid the possibility of a Valsalva effect. A reading was taken at the beginning and end of a 3-minute rest period. At the end of a normal expiration the subject was asked to stop breathing. The procedure was timed so that systolic and diastolic readings were taken after approximately 20 seconds of breath-holding. This generally meant that the systolic level was recorded just before, and the diastolic just after, the intended interval, so that the total holding time was slightly over 20 seconds. During the recovery period following the breath-holding stimulus, three readings were taken at 1-minute intervals. Our procedure differed from that of Ayman and Goldshine[14] in that they used separate periods of breath-holding to determine the systolic and the diastolic blood pressure. Although the accuracy of measurement is improved by their method, the interpretation of results is more difficult because of the double stimulus.

***A further description of the procedure, with enumeration of the successive blood pressure readings to correspond to the numbers in Figs. 2-4, is included in the appendix.**

†Hereafter "reading" will signify a determination of systolic and diastolic blood pressure and pulse rate.

Exercise Test.—Following appropriate instructions to the subjects, blood pressure readings were taken before and after a 3-minute rest period with the subjects in the seated position. Then the subject stood, hands on hips, and alternately flexed and straightened his knees in time with a metronome 30 times in 60 seconds. The blood pressure and pulse rate were taken with the subject in the seated position immediately after and at 1-minute intervals for 3 minutes following the stimulus.

Definition of Terms.—Test responses were calculated from the difference between blood pressure and pulse rates immediately before and at the time of maximal stimulation. In the postural test the first reading taken with the subject standing erect was compared to the last measurement in recumbency. The response to rest was defined as the difference between the first and the last recumbency readings obtained 23 minutes later.

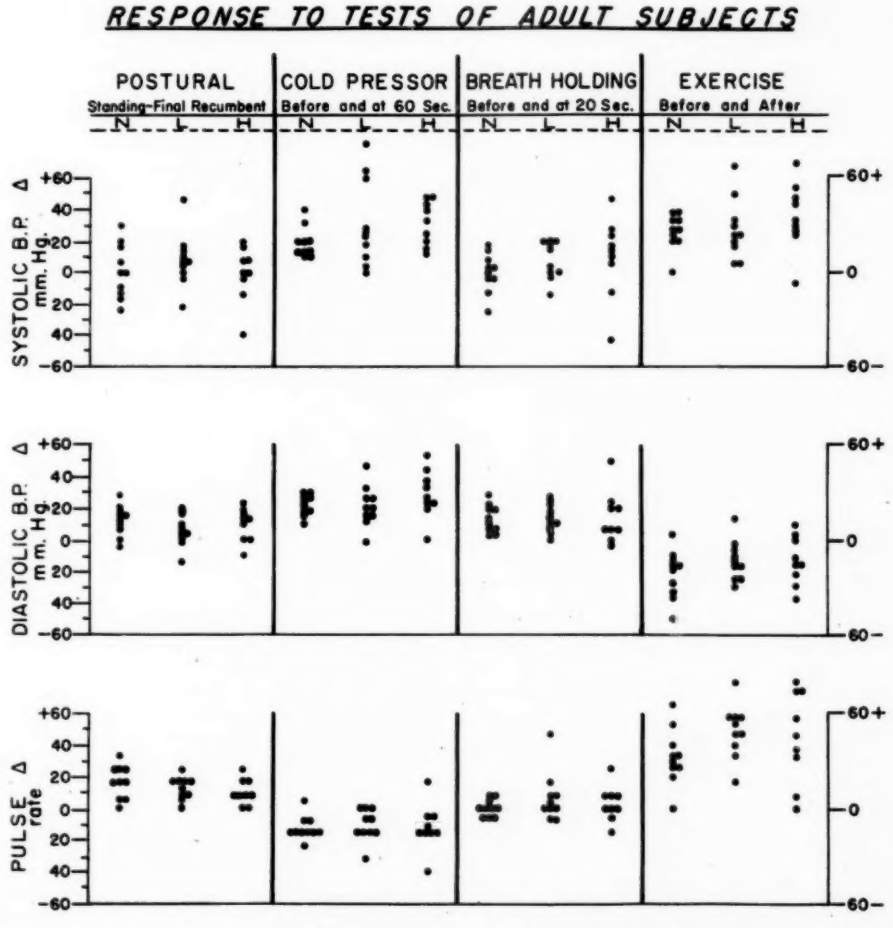

Fig. 1.—The entire test series was performed on 10 normotensive (*N*—first column), on 10 labile (*L*—second column), and on 9 established hypertensive (*H*—third column) subjects. The vertical scale represents change (Δ) in blood pressure and pulse following the application of the various tests.

OBSERVATIONS

a. *Reproducibility of the Tests.*—In order to estimate the degree of reproducibility in the same person the tests, with the exception of the postural test, were performed on four medical students on six occasions in a randomly selected order of administration. There was no apparent day-to-day variation in the responses

and no evidence of a systematic effect of any one test on subsequent ones. The mean systolic, diastolic, and pulse responses and standard deviation of each test in the four subjects were as follows: *Cold Immersion:* systolic, 26 ± 10; diastolic, 33± 9; pulse, −6 ±7. *Breath-Holding:* systolic, 5 ± 10; diastolic, 7 ± 10; pulse, 5 ± 11. *Exercise:* systolic, 15 ± 11; diastolic, −16 ± 14; pulse, 50 ± 7. To obtain the standard error of each mean, the standard deviation is divided by $\sqrt{24} = 4.9$.

b. *Responses of Adult Subjects With and Without Hypertension.*—The mean responses of each group to each test are listed in Table II. The range of individual responses is shown in Fig. 1. There appears to be no consistent difference in the response of the normotensive, labile, or established hypertensive subject, nor between these groups and the groups of children (Groups I, II, and III).

TABLE II. MEAN TEST RESPONSES OF THE STUDY GROUPS

GROUPS	REST		POSTURAL		COLD		BREATH-HOLDING		EXERCISE	
	BLOOD PRESSURE (MM. Hg) S*/D*	PULSE RATE	BLOOD PRESSURE (MM. Hg) S/D	PULSE RATE	BLOOD PRESSURE (MM. Hg) S/D	PULSE RATE	BLOOD PRESSURE (MM. Hg) S/D	PULSE RATE	BLOOD PRESSURE (MM. Hg) S/D	PULSE RATE
Normotensives	−10/−1	−8	1/12	16	19/23	−13	0/13	0	26/−21	32
Labile Hypertensives	−15/−3	−4	8/7	12	31/21	−11	8/13	7	28/−14	48
Established Hypertensives	−10/−9	−7	0/9	10	31/28	−13	9/15	3	36/−14	45
Children of Normotensive Parents	−10/+2	−3	3/13	10	12/25	− 7	7/17	−7	18/−21	29
Children of Hypertensive Parents	−12/+2	−4	7/13	12	11/24	− 5	8/15	−5	19/−21	27
Children of Bahamian Parents	−14/−2	−8	4/15	7	11/19	−11	8/16	0	20/−26	23

*S = Systolic. D = Diastolic.

Rest response represents the decline in blood pressure between final recumbent reading (reading No. 9 in Fig. 2) and the first recumbent reading (No. 2). Postural response is defined as the first standing reading in the postural test (No. 10) minus the final recumbent reading (No. 9). Cold response represents the difference between the reading after 60 seconds of ice-water immersion (No. 17) and the pressure immediately prior to immersion (No. 15). Breath-holding and exercise responses likewise represent the difference in blood pressure after and before maximum stimulation (Nos. 23-22 and Nos. 29-28, respectively).

It was recognized that the rest period prior to cold immersion was abbreviated and that a greater response might have appeared if this part of the test had not been omitted. However, if the reading after 23 minutes of rest (No. 17) is subtracted from the maximum rise after ice-water stimulation (No. 9), the increments in blood pressure due to the cold stimulus are not greatly different and the averages for each group are: Normotensives = 24/25, Labile Hypertensives = 31/25, Established Hypertensives = 42/33, Children of Normotensives = 18/30, Children of Hypertensives = 21/29, and Children of Bahamian Parents = 15/22.

c. *Blood Pressures of the Offspring of Normotensive and Hypertensive Parents.*—Table II and Figs. 2, 3, and 4 present the mean systolic and diastolic blood pressure and the mean pulse rates of Groups I, II, and III at various points in the test procedure. The order of statistical significance of the differences in blood pressure and pulse readings between Groups I and II is indicated at the bottom of the figures. It will be seen that the offspring of hypertensive subjects (Group

II) had a higher average systolic pressure and a lower average pulse rate than did their counterparts in Group I, and that these differences were statistically significant ($P < .05$) at nearly every point in the test procedure. In contrast, the diastolic blood pressures of the two groups did not differ significantly from each other.

It may be noted in passing that the "potentially hypertensive" young people exhibited the widest deviation from the offspring of normotensive parents in systolic blood pressure readings Nos. 14, 15, and 26. At these points the difference between the respective mean systolic readings were of the order of 8 mm. Hg. The probability was less than one in a thousand that these differences were due to chance. The readings taken just before the cold pressor test (Nos. 14 and 15) might be considered to reflect an undue rise in blood pressure in the prehypertensive group as a result of the contemplation of an ensuing unpleasant stimulus.

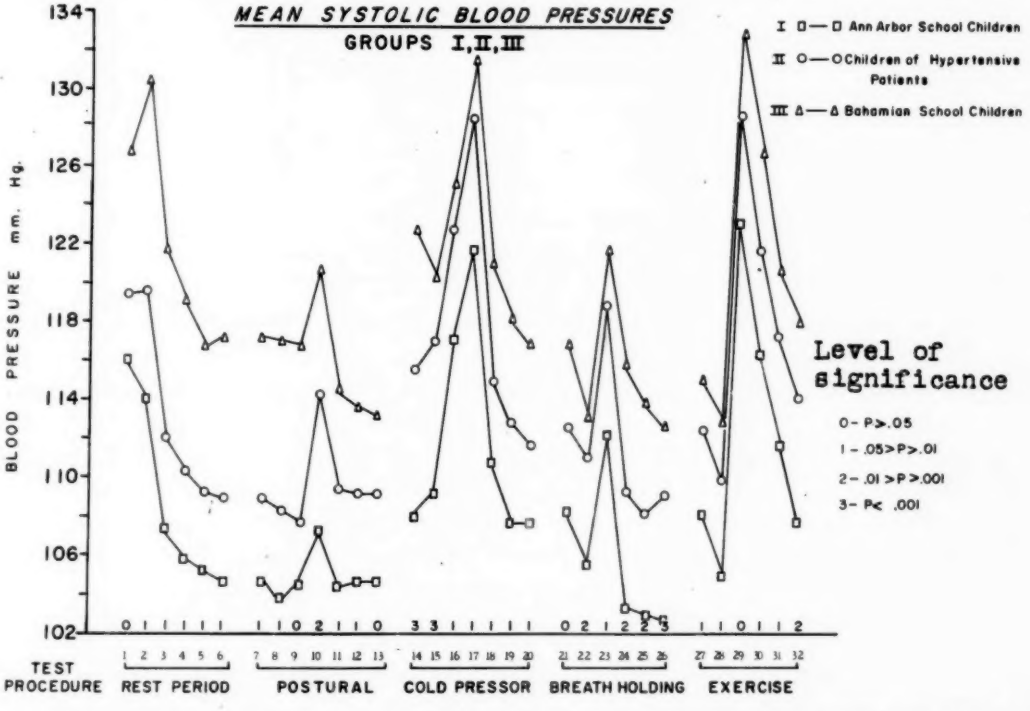

Fig. 2.—On the horizontal scale the degree of significance of the differences between readings for Groups I and II is recorded. Although Group III is included for comparison, the selection of the Bahamian Negro children was less rigorously controlled and the status of blood pressure of the parents was unknown.

However, no such excessive reaction was observed prior to the postural or exercise tests. It is also of interest to note that no significant difference between the group means was observed in the casual reading taken with the subjects standing (No. 1), in the final observation on resting recumbency (No. 9), and in the reading taken immediately after exercise (No. 29).

On further analysis it was found that the five individuals in Group II with the highest resting systolic blood pressure readings tended to show less fluctuation at every point in the test series, whereas those subjects with lower resting blood

pressures were found to exhibit greater variability from test to test. These observations are of interest since not all subjects in Group II may be expected to develop hypertension, but those with the highest blood pressure would seem a priori to be the most likely candidates.

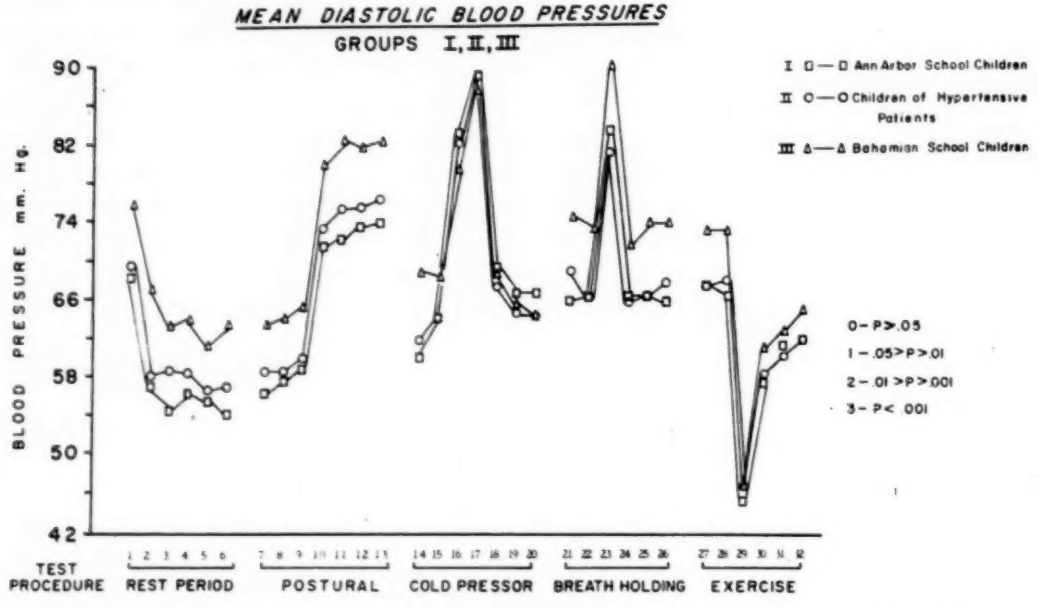

Fig. 3.—Details are as in Fig. 2. No significant difference between Groups I and II is observed.

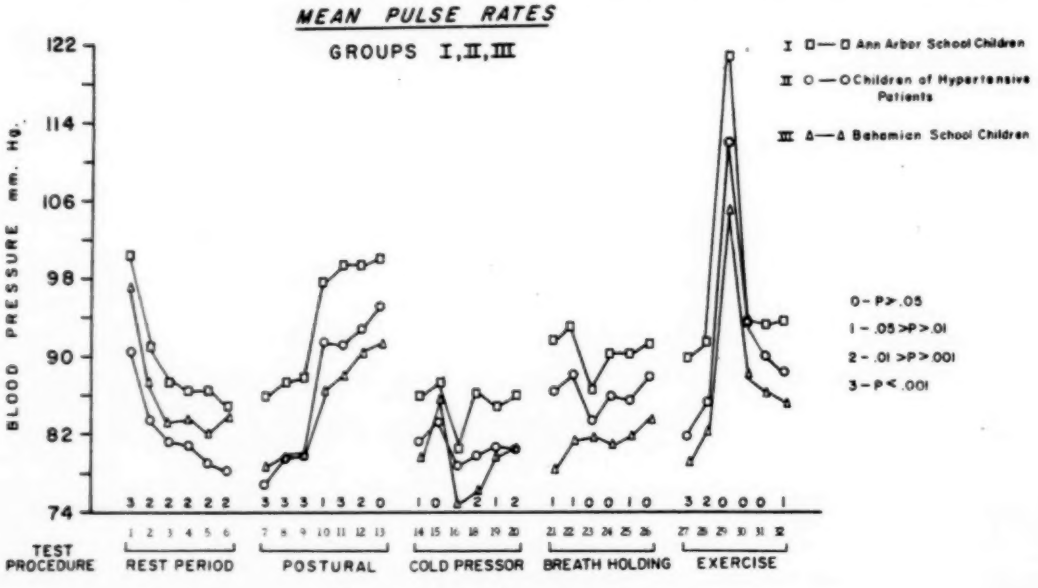

Fig. 4.—Details are as in Fig. 2.

The Bahamian subjects were not included in the statistical comparison because the test conditions were somewhat different, and because they were not individually matched with the subjects in Group I, although they were of similar age and sex distribution (Table I). Nevertheless, Fig. 2 shows that the

mean systolic blood pressure of these subjects was slightly higher at every point in the series than that recorded for Group II, and considerably in excess of that for Group I. Their mean pulse rate (Fig. 4) was lower than that of Groups I or II, whereas no difference in diastolic levels was observed. These observations, carried out under quite different surroundings, are also consistent with the view that a higher average blood pressure has already become apparent in this group of "potentially hypertensive" subjects.

An analysis of the test responses of the paired groups and of the Bahamian children is also recorded in Table II and in Figs. 2-4. No significant difference in vascular reactivity between Groups I and II could be detected, except that in the postural test, Group II showed a significantly ($P < .05$) greater rise in mean systolic blood pressure than did Group I.

d. *Relation of Physical Characteristics of the Children to the Blood Pressure Reading.*—The possibility that group differences in age, arm girth, or sex influenced the results was considered. A study of the coefficients of regression for each variable demonstrated no significant trend with age or arm girth for any age-sex subgroup, but the small number involved in these subgroups ($N = 14$ to 24) made the demonstration of a significant difference improbable even if small effects had existed.

Inspection of the data recorded in graphic form showed a slight tendency for the mean blood pressure to increase with age. This change occurred equally in Groups I, II, and III. The increase was not the direct result of increased arm girth or of an unusual increase in blood pressure in either boys or girls. The slight increase in the mean blood pressure with age appeared to result more from a few higher individual readings than from a general upward tendency for all subjects. The few individuals under the age of 11 showed generally lower readings. In six of these a child-size cuff was used. Since these impressions are derived from small samples and within a very limited age range, it is of course impossible to draw any conclusions concerning the effects of these physical factors on the blood pressure readings except to state that they did not appear to be responsible for the observed differences between the three groups.

DISCUSSION

From these studies it is concluded that the response to no test or combination of tests which we used is characteristic of the hypertensive as compared to the normal individual. Whereas in established hypertensive subjects, abnormal reactivity to pressor stimuli might be obviated by permanent vascular changes, the tests in labile hypertensive patients should demonstrate abnormal responses if increased reactivity is a characteristic of "early" hypertension. The presence of a number of hyporeactors among labile hypertensive subjects certainly indicates that these tests do not consistently identify the labile hypertensive subject.

It is possible that some factor in the selection of control subjects obliterated differences in the reactivity of the various adult groups tested. The rise in blood pressure of the normal subjects in response to cold immersion was, in fact, greater than that reported by Hines and Brown[9,10] for normotensive individuals.

Laboratory workers in a hospital might be expected to show less reaction to such stimuli than would unselected normal subjects. The shortening of the rest interval might result in a higher "pre-test" blood pressure in the hypertensive than in the normal subject, so that differences would be abolished. To evaluate this possibility we calculated the difference between the blood pressure taken after 60 seconds of cold stimulation (No. 17) and the blood pressure recorded after 23 minutes of quiet recumbency (No. 9). These differences did not help to separate the normotensive, labile, and established hypertensive groups. We must conclude, therefore, that no single test is useful in identifying the hypertensive subject. This conforms with the experience of others.[7,11,12]

In consequence, it would not be expected that the children of hypertensive parents would display hyperreactivity to similar stimuli. A close examination of the responses of the children with the highest resting blood pressures likewise revealed that these potentially hypertensive subjects showed no evidence of consistent vascular hyperreactivity.

It was of interest, however, to observe a higher mean systolic blood pressure in the children of hypertensive parents. Moreover, inspection of the data provided by Miall and Oldham[1] reveals a similar tendency. Twenty-nine children having a parent with a blood pressure of 150/100 mm. Hg or more were compared with 72 children whose parents had blood pressures not higher than 140/90 mm. Hg. The children having one hypertensive parent had mean systolic and diastolic blood pressures of 119/74 mm. Hg, whereas the corresponding means for the children of normal parents were 112/72 mm. Hg. The systolic means are highly significantly different ($P < .005$), whereas the diastolic means are not significantly different ($.20 > P > .10$). It is interesting to note how closely these observations of Miall and Oldham parallel those of the present study.

Such comparable results lend greater support to what would at first glance appear to be only slight differences in the blood pressure of the offspring of hypertensive subjects. After prolonged rest, the children of a hypertensive parent had a mean blood pressure of 108/60 mm. Hg as compared to 104/59 mm. Hg for the offspring of normotensive parents. The difference in mean systolic pressure achieves statistical significance ($P \leqq .05$). Furthermore, since a consistent and significant difference was found in almost every one of the 32 consecutive systolic readings, it is hardly likely that the differences were due to chance alone. It is of further interest that the maximum difference (8 mm. Hg) between the two groups occurred in the blood pressure just prior to the cold pressor stimulus; it suggests that the blood pressure response to a mental stimulus may be excessive in the potentially hypertensive as opposed to the normal subject.

The possibility that intentional bias on the part of the examiner led to the observed differences seems unlikely because of the failure to observe differences in the diastolic blood pressure. If the children of hypertensive parents were more apprehensive about the tests and thus displayed a higher blood pressure, one would expect a greater mean pulse rate in this group. That the contrary was observed would seem to dispose of this objection. The evidence therefore seems convincing that teen-age children with a single hypertensive parent already exhibit a tendency to a higher average systolic blood pressure.

If the expected frequency of future hypertension in children with one hypertensive parent were about 30 per cent,[3] then 70 per cent of the subjects in Group II should behave normally, and only a slight elevation in the mean blood pressure would be expected to appear. The characteristics of the five individuals in Group II (those of hypertensive parentage with the highest resting systolic blood pressure levels) were contrasted with the characteristics of the five children of Group I who had the highest resting systolic pressures. Those in Group II had a resting systolic reading in excess of 118 mm. Hg as compared to 104 mm. Hg for those of Group I, the control group. They tended to remain consistently at the top of Group II during stimulation and during rest.

The presence of a higher average systolic blood pressure and a lower pulse rate in the children of hypertensive parentage is the most important finding in this study. It is especially interesting that this difference is maintained under all forms of stimulation tested, and during rest, whether sitting, standing, or lying. Both the Michigan and Bahamian study groups show this characteristic. It is possible that a slow pulse rate was the primary abnormality which resulted in a higher stroke volume and, as a consequence, an increased systolic blood pressure. It would then be necessary to assume that bradycardia is an early sign of hypertension. Since a slow pulse is not seen in manifest forms of hypertension and is, in any event, unlikely to affect cardiac output and pulse pressure to the extent observed, such a hypothesis seems improbable.

An increase in stroke volume might be considered a primary event in the genesis of hypertension. This theory[18] once widely held has since been abandoned in view of anatomic and physiologic evidence for an increase in peripheral resistance in hypertension.

A third explanation might be that a slight increase in vascular rigidity is already apparent in the offspring of hypertensive parents, and that this leads to a widened pulse pressure and reflex cardiac slowing. Conway[19] has suggested that some subjects with hypertension, in whom a family history of the disease is prominent, may, in fact, exhibit high blood pressure because of altered arterial and arteriolar elasticity rather than as a result of functional arteriolar vasoconstriction.

These hypotheses concerning the pathogenetic mechanism of familial hypertension must remain speculative so far as the present study is concerned. The principal conclusion to be derived from this report is that response of the blood pressure to stimulation is certainly no more indicative, and possibly even less indicative, of latent or overt hypertension than is the actual level of systolic blood pressure.

CONCLUSIONS

1. Four tests of vascular reactivity—postural change, cold immersion, breath-holding, and exercise—were applied to 10 normotensive, 10 labile hypertensive, and 9 fixed hypertensive subjects. No consistent differences between the groups were observed.

2. The same tests were applied to 50 children, aged 8 to 18, of hypertensive parents matched with 50 children of normal subjects. They were also applied to

31 Negro children of comparable age in an area with a high prevalence of hypertension. No evidence of unusual vascular hyperreactivity was observed in children of hypertensive parentage, with the possible exception of the response of systolic blood pressure to postural change.

3. The mean systolic blood pressure of the offspring of hypertensive parents was significantly higher at all stages of testing than that of the children of normotensive parents. Furthermore, an analysis of published reports of the data of other investigators confirms that a slight but statistically significant elevation of systolic blood pressure occurs in the youthful offspring of hypertensive subjects.

4. The pulse rate of the children of hypertensive parents (Group II) was significantly lower than that of the children of normotensive parents (Group I), but the mean diastolic pressure of the groups did not differ. Possible explanations of these observations are discussed.

5. It is concluded that a systolic blood pressure in the high "normal" range appears at puberty in certain offspring of hypertensive parents, but that conventional tests of vascular reactivity are not of great usefulness in selecting children likely to develop hypertension.

APPENDIX

Protocol for Blood Pressure Reactivity Tests

TEST PROCEDURE	PROCEDURAL STEP	SUBJECT'S POSTURE	OBSERVATION NO.	
	Subject enters room	Standing	1	
	Subject lies on bed	Lying	2	
Rest Period	After 5 minutes' rest	Lying	3	
	After 10 minutes' rest	Lying	4	
	After 15 minutes' rest	Lying	5	
	After 20 minutes' rest	Lying	6	
	After 21 minutes' rest	Lying	7	
	After 22 minutes' rest	Lying	8	
	After 23 minutes' rest	Lying	9	
Postural Test	Subject stands	Standing	10	
	After standing 1 minute	Standing	11	
	After standing 2 minutes	Standing	12	
	After standing 3 minutes	Standing	13	
Cold Pressor Test	Subject lies on bed	Lying		
	Cold pressor test explained	Lying		
	After explanation	Lying	14	
	Ice water brought in	Lying		
	3 minutes after explanation	Lying	15	
	Right hand immersed in ice water	Lying		
	After 30 seconds' immersion	Lying	16	Blood pressure only
	After 60 seconds' immersion	Lying	17	Blood pressure only
	After removal of hand from water	Lying	17	Pulse rate only
	1 minute after removal	Lying	18	

	2 minutes after removal	Lying	19	
	3 minutes after removal	Lying	20	
Breath-Holding Test	Subject sits in chair	Sitting		
	Breath-holding test explained	Sitting		
	After explanation	Sitting	21	
	3 minutes after explanation	Sitting	22	
	Subject holds breath	Sitting		
	After 20 seconds' breath-holding	Sitting	23	Blood pressure only
	After resumption of breathing	Sitting	23	Pulse rate only
	1 minute after resumption	Sitting	24	
	2 minutes after resumption	Sitting	25	
	3 minutes after resumption	Sitting	26	
Exercise Test	Exercise test explained	Sitting		
	After explanation	Sitting	27	
	3 minutes after explanation	Sitting	28	
	Subject exercises (30 deep knee bends)	Standing		
	Immediately after exercise	Sitting	29	
	1 minute after exercise	Sitting	30	
	2 minutes after exercise	Sitting	31	
	3 minutes after exercise	Sitting	32	

The cold pressor test, breath-holding test, and exercise test were given to our subjects in a preselected, random order, determined by consulting a random number table. The numbers in the column headed *Observation No.* refer to Figs. 2, 3, and 4, and are also discussed in the text.

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Normal Variants in the Electrocardiogram Leading to Cardiac Invalidism

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In spite of the fact that the electrocardiogram is merely a laboratory test and rarely the sole means of arriving at a cardiac diagnosis, it is unfortunate that erroneous interpretations of the electrocardiogram do occur and lead to cardiac invalidism in normal individuals. Prinzmetal[1] estimates that an average physician caring for cardiac patients sees 10 to 25 cases of "heart disease of electrocardiographic origin" per year.

The QRS complex of the electrocardiogram is reasonably well understood. However, this is not true for the S-T segment and the T wave. Departure from the assumed normal of these latter components of the electrocardiogram does not always mean an abnormality of the myocardium. In addition to the known myocardial disease states which produce S-T segment and T-wave abnormalities, many extracardiac causes are well recognized. These include: (1) the effect of drugs, (2) electrolyte imbalance, (3) postprandial changes which are probably related to potassium shifts,[2] (4) drinking ice water, (5) the juvenile pattern in young adult Negroes,[3] and (6) autonomic nervous system imbalance caused by emotional influences.[4,5] In this latter category can be included the electrocardiographic changes occurring following hyperventilation and the abolishment of these changes after the administration of vagal blocking drugs.[6] In addition, changes in the S-T segment and T wave have been described for which there is no known pathologic, physiologic, or biochemical explanation. S-T segment elevations, up to 4 mm. in mid- to left precordial leads, simulating pericarditis, can occur in normal individuals. Characteristically these S-T changes temporarily return to the isoelectric line following exercise.[7,8] Negative T waves in one or more precordial leads (V_3 to V_6) occurring in normal individuals have been referred to by Grant as the isolated T-negativity syndrome.[9] The mechanism of this syndrome is unknown. Grant explains this finding on the basis of electrical forces generated from a superficial region of the heart which are too small in magnitude to be recorded in more remote body surface leads, but are so near the chest wall that they predominate in these certain precordial leads. He considers this as one circumstance in which body surface deflections are not in accord with the spatial vector concept.

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It is the purpose of this article to report 5 patients whose electrocardiograms showed gross S-T segment and T-wave changes, admittedly indistinguishable from similar tracings resulting from organic heart disease. In all 5 patients there were no other clinical signs of heart disease, and the "abnormal" electrocardiographic pattern remained unchanged over periods of 1 to 3 years. Two of these patients were made cardiac invalids, and one was subjected to thoracotomy and pericardial biopsy solely on the basis of the electrocardiographic findings.

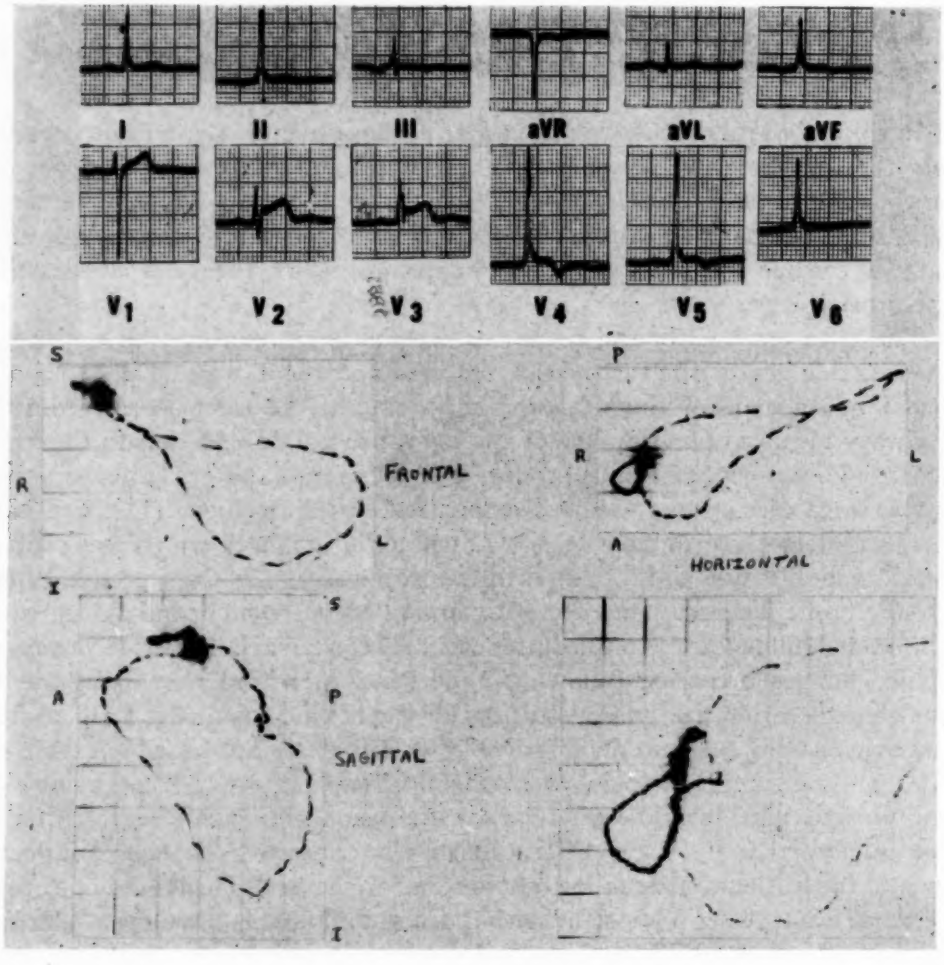

Fig. 1.—Electrocardiogram and spatial vectorcardiogram in Case 1. The electrocardiogram shows S-T segment elevation in Leads V_2 through V_4, inverted T waves in V_4 and V_5, and diphasic T waves in aVF and V_6. The voltage of $R_{V5} + S_{V1} = 41$ mm. Whereas this voltage would be indicative of left ventricular hypertrophy in an older individual, it is not diagnostic in a 22-year-old individual. Furthermore, there was no other clinical evidence of, or reason for, left ventricular hypertrophy in this patient. The electrocardiographic pattern was not altered by basal conditions, exercise, or Pro-Banthine. The spatial vectorcardiogram was recorded using the Frank lead system. The tail of the dash indicates the direction of the vector loop. The QRS loop is normally inscribed and is oriented inferiorly, to the left and slightly posterior. The QRS loop fails to close prior to inscription of the T loop, resulting in an S-T vector oriented to the left and anteriorly. This is best seen in the horizontal projection. The T loop is oriented to the right, anteriorly and slightly superior. This results in an abnormal QRS-T angle. A similar vectorcardiogram was recorded with the cube system.

CASE REPORTS

CASE 1.—S. M., Negro, male, age 22. Three years previously, at age 19, the patient had experienced a one day's illness characterized by fever, generalized muscle aching, and some discomfort in the anterior chest. As part of a complete examination an electrocardiogram was taken, and the patient was immediately hospitalized and told that he had suffered a myocardial infarction. This at once ruined a promising career in professional football. When first seen at this hospital 3 years later, he admitted to no further symptoms. He had had considerable trouble gaining employment because of the above-mentioned history. Physical examination revealed a muscular young Negro. No abnormalities could be detected. Roentgenograms of the chest were normal. The electrocardiogram and spatial vectorcardiogram are illustrated in Fig. 1. The clinical records and electrocardiograms were then obtained from the hospital which had cared for him 3 years previously. There had been no clinical evidences of heart disease other than the electrocardiographic "abnormality," and all electrocardiograms over the 3-year interval showed no change. The electrocardiogram remained unchanged under basal conditions, after eating, and after exercise. In view of the clinical absence of heart disease and a stationary electrocardiographic pattern for 3 years, it must be concluded that the latter is a normal variant. An attempt is being made to convince the patient of this and to help him in obtaining employment.

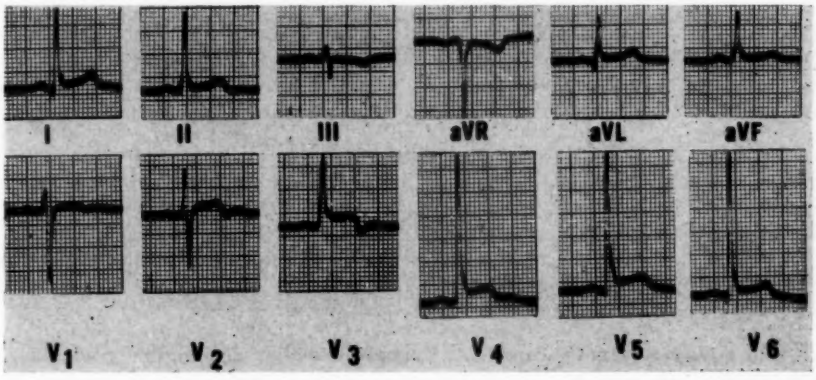

Fig. 2.—Electrocardiogram in Case 2. There is S-T segment elevation in Leads V_2 through V_6, with late T-wave inversion from V_1 through V_3. The maximal changes are seen in Lead V_3. The R voltage in V_6 = 31 mm. The voltage of $R_{V6} + S_{V1}$ = 46 mm. These voltage criteria would indicate left ventricular hypertrophy in an older individual but are not diagnostic in a 24-year-old individual. Furthermore, there was no other clinical evidence of left ventricular hypertrophy.

CASE 2.—B. E., Negro, male, age 26. Two years previously, while in the military service, the patient one day complained of a sticking precordial pain. An electrocardiogram was taken, and the patient was immediately hospitalized. A review of the hospital records revealed the fact that the attending physicians could find no clinical evidence of heart disease. After a 4-month period of observation the electrocardiographic pattern remained unchanged. In spite of this a diagnosis of pericarditis was seriously entertained. A left thoracotomy was done. Grossly, the heart and pericardium were normal. A pericardial biopsy was normal. When he was first seen at this hospital 2 years later, there was no evidence of heart disease on the basis of history, physical examination, and roentgenograms of the chest. The electrocardiogram (Fig. 2) was unchanged from those prior to thoracotomy and pericardial biopsy.

In this instance, solely on the basis of an unchanging electrocardiographic pattern, the patient had been subjected to thoracotomy and pericardial biopsy. The difficulties now encountered in explaining the facts to the patient and in rehabilitating him from cardiac invalidism are obvious.

CASE 3.—A. F., Italian, male, age 26. This individual entered the Oakland Veterans Administration Hospital because of a cellulitis of the right leg; the condition cleared within 4 days of treatment consisting of rest and penicillin. The patient gave a history suggestive of rheumatic fever 10 years previously, but he had no knowledge of having rheumatic heart disease. Physical

examination revealed no cardiac abnormalities. Roentgenograms of the chest were normal. The electrocardiogram is seen in Fig. 3,*A*. Because of the history of rheumatic fever and the recent cellulitis, a diagnosis of active rheumatic myocarditis was initially considered. However, over a 3-week period of observation there never were any abnormalities on physical examination of the heart, and all laboratory studies, including antistreptolysin titers, throat cultures, and sedimentation rates, revealed no abnormalities. Serial electrocardiograms were unchanged from that shown in Fig. 3,*A*. An electrocardiogram was then taken under basal conditions (Fig. 3,*B*) and was normal.

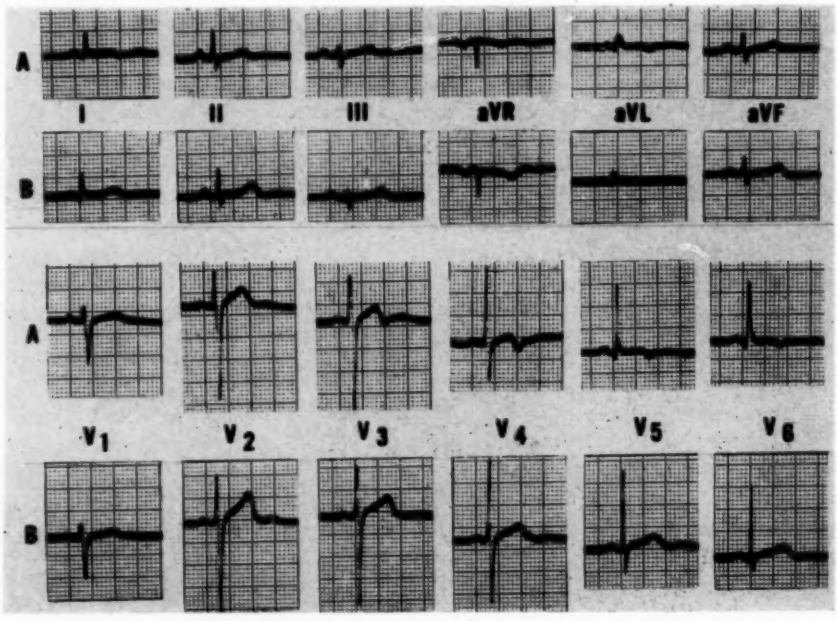

Fig. 3.—Electrocardiograms in Case 3. *A*, Tracings taken at random, under nonbasal conditions. Also, the pattern after: (1) exercise, (2) eating, and (3) hyperventilation, each done individually following a basal electrocardiogram. This tracing illustrates T-wave inversion in Leads aVL, and V_4 through V_6. The T waves are diphasic in Leads I and V_3. *B*, Tracings taken under basal conditions. Also, this pattern persisted in spite of exercise, eating, and hyperventilation, when these maneuvers were preceded by Pro-Banthine. The electrocardiogram is within normal limits.

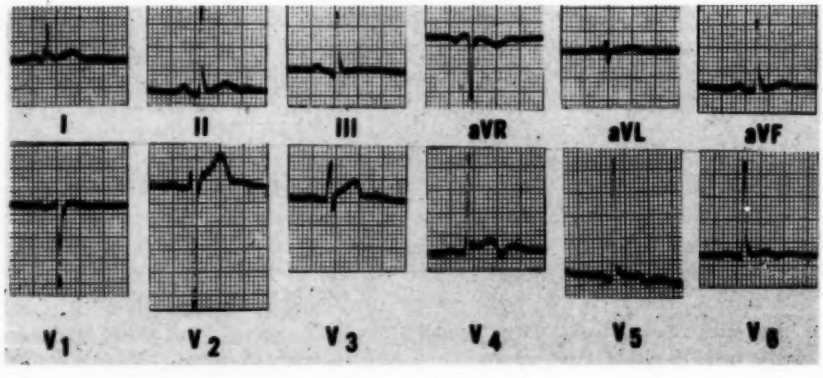

Fig. 4.—Electrocardiogram in Case 4. This tracing shows S-T segment elevation in Leads V_2 through V_5 and late T-wave inversion from V_4 through V_6. The voltage of $R_{V5} + S_{V1} = 41$ mm., but the patient was 24 years of age and there were no other clinical signs of left ventricular hypertrophy. The electrocardiographic pattern was not altered by basal conditions, exercise, or Pro-Banthine.

On subsequent days, with a normal basal electrocardiogram, a repeat electrocardiogram was taken individually after: (1) eating, (2) mild exercise, and (3) hyperventilation. After each of these tests the electrocardiographic pattern reverted to that seen in Fig. 3,*A*. On a subsequent day, with a normal basal electrocardiographic record, the patient was given 30 mg. of Pro-Banthine orally. After 45 minutes the patient was subjected to the same tests mentioned above, and no changes developed in the electrocardiogram. This is the only instance in this series of patients in which the electrocardiographic pattern could be altered by such maneuvers. In a 1-year follow-up the patient has remained clinically well. The same T-wave abnormalities persist in tracings taken under nonbasal conditions. The patient has been informed of the findings and impressed with the fact that they do not indicate heart disease. He has been advised to have any doubtful employer or physician contact this hospital.

CASE 4.—Negro, male, age 24. (See Fig. 4.)

CASE 5.—Negro, male, age 26. (See Fig. 5.)

In Cases 4 and 5, electrocardiograms were taken on the patients merely as a routine test. In neither patient was there any clinical evidence of heart disease. The electrocardiograms were not altered under basal conditions, exercise, or following Pro-Banthine. During a 2-year period of observation, the electrocardiograms have remained unchanged, and clinically the patients are in excellent health. Again, these patients have been informed of the findings and the same advice given as in Case 3.

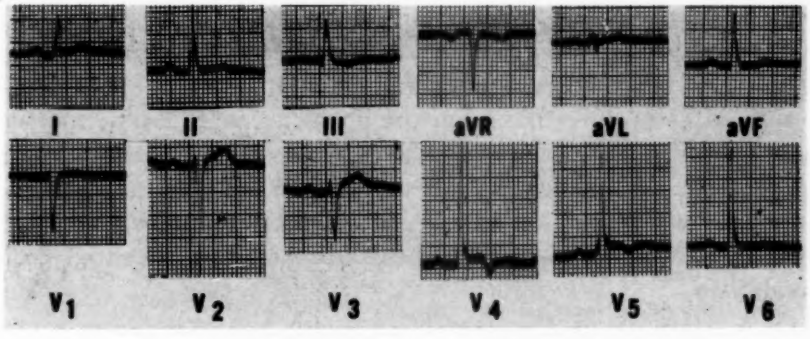

Fig. 5.—Electrocardiogram in Case 5. There is S-T segment elevation from V_2 through V_5, with deep T-wave inversion in V_4 and V_5 and a diphasic T in V_6. The voltage of $R_{V5} + S_{V1} = 38$ mm. The electrocardiographic pattern was not altered by basal conditions, exercise, or Pro-Banthine.

DISCUSSION

An electrocardiographic pattern is described which by ordinary criteria would be considered abnormal. However, in none of the 5 patients was there any other clinical evidence of heart disease. Follow-up examinations over a period of 1 to 3 years have failed to reveal any clinical evidence of heart disease, and the electrocardiographic pattern has remained unchanged. The electrocardiographic features are: (1) S-T segment elevation, with a concave configuration in precordial leads from V_3 through V_6; (2) T-wave inversion in one or more of the above-mentioned precordial leads, in association with S-T segment elevation in 4 patients and without S-T segment change in 1 patient; (3) no change in the electrocardiographic pattern of those patients with both S-T segment and T-wave changes under basal conditions or following eating, exercise, or Pro-Banthine; (4) reversion to a normal electrocardiogram in the 1 patient with T-wave changes alone when the electrocardiogram was taken under basal conditions, and the prevention by Pro-Banthine of the changes induced by eating, exercise, and hyperventilation;

and (5) voltage criteria[10] which in older individuals would be indicative of left ventricular hypertrophy, but which are not diagnostic in these patients because of their youth. Furthermore, in no instance was there any other clinical evidence of, or reason for, left ventricular hypertrophy.

The lack of change in the S-T segment following exercise in the patients with both S-T and T changes is in contrast to the reports of normal individuals with S-T segment changes only. In the latter, exercise invariably brought the S-T segment to the isoelectric line. The mechanism for the change in the latter group and the lack of change in the cases illustrated in this report is unknown.

The T-wave changes cannot be explained by Grant's explanation of isolated T negativity. If this were true, spatial vectorcardiograms should show normal T loops. However, in the spatial vectorcardiogram illustrated in Case 1 (and in those of 2 other patients, which are not reproduced), taken by the Frank and cube systems, the T loops were oriented to the right, anteriorly and slightly superior, resulting in an abnormal QRS-T angle.

The point to be emphasized is that an electrocardiogram demonstrating only S-T segment and T-wave changes should never be the sole criterion for the diagnosis of heart disease. Sound clinical evaluation of the patient based on a careful history, physical examination, and pertinent laboratory data must be correlated with the electrocardiogram. Admittedly, when an electrocardiogram similar to those illustrated is first seen, the physician will become alerted to the possibility of organic heart disease.[11] However, this problem can be resolved by the absence of other clinical evidences of heart disease and the unchanging electrocardiographic pattern on serial tracings. If this is not appreciated, the patient will be informed that he has organic heart disease and relegated to a life of cardiac invalidism.

SUMMARY

1. Five patients are presented whose electrocardiograms showed "abnormalities" in the S-T segment and T wave.

2. The electrocardiographic pattern remained unchanged over periods of observation ranging from 1 to 3 years.

3. In no patient were there other clinical signs of heart disease.

4. Two patients were made cardiac invalids, and one patient was subjected to thoracotomy and pericardial biopsy solely on the basis of an unchanging electrocardiographic pattern.

5. Correlation of the electrocardiogram with clinical evaluation of the patient is essential for correct diagnoses.

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Experimental and Laboratory Reports

The Hibernating Mammalian Heart

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INTRODUCTION

It has long been known that the hibernating mammal can be decapitated, and its essentially denervated heart continues to beat in the corpus for a long period of time (Mangili,[1] Merzbacher,[2] Johnson[3]). It can also be shown that if the heart is removed from a hibernating mammal and placed in cold physiologic saline at about 5°C., it will continue to beat for a much longer period of time than the heart removed from a nonhibernator treated similarly. These phenomena give rise to some speculations with reference to maintenance of viability of this heart: (a) What are the temperature characteristics of hibernating hearts? (b) Is it correct to say that tissue which is removed from a hibernating animal "hibernates"? (c) Is this behavior of a denervated hibernating heart in the cold an essential physiologic prerequisite for the phenomenon of natural mammalian hibernation?

METHOD

Thirteen-lined ground squirrels (*Citellus tridecemlineatus*) were maintained in hibernacula which featured conditions favoring hibernation, that is, confinement, isolation, darkness, quiet, and a temperature close to 5°C. Small stainless steel wire electrodes were chronically implanted in the skin of the right shoulder and both thighs. The animals cycled in and out of the hibernating state from late autumn throughout the winter and into early spring. When in deep hibernation, an animal was moved to a specially designed cold chamber in the laboratory, where wires were clipped to the electrodes in order to take Lead II electrocardiograms.

Experiments were performed on decapitated ground squirrels (in which the heart was functionally isolated from the brain, and the circulatory system was severely disrupted) and on isolated ground squirrel hearts (in which all connections with the body were eliminated). Eighteen animals

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were decapitated in all, some in deep hibernation, some after arousal had proceeded to a particular stage (as determined by the body temperature measured under the skin of the shoulder), and some in normal activity (during the nonhibernating season). In each experimental case the corpus was placed in the cold chamber and the activity of the heart was followed continuously on the electrocardiograph. Electrocardiograms were taken before, during, and after decapitation. In six cases, after the animal was beheaded in deep hibernation, the heart was quickly excised and isolated and placed in cold unoxygenated physiologic saline at 5°C. Electrical activity of the isolated heart was recorded on the electrocardiograph from stainless steel electrodes immersed in the cold saline. Contraction of the heart was determined visually.

Four white rats also were decapitated and the hearts of three of these were excised and electrocardiograms taken.

RESULTS

The decline in temperature of the decapitated body placed in a 2°C. chamber is shown in Fig. 1. The warmer the animal at the time of decapitation, the faster the initial rate of cooling. Within an hour after decapitation, all corpora had cooled to a temperature close to 10°C. Thereafter cooling was very slow.

Heart rates after decapitation in hibernation or arousal from hibernation are shown in Fig. 2. The rate fell precipitously during the first 20 minutes to about 30 beats per minute. Thereafter the heart continued to beat for several hours at a very slowly declining rate. All hearts behaved similarly, regardless of the state of arousal. On the other hand, the heart of a nonhibernator (white rat) showed the same rapid decrease in rate, but it progressed until the heart completely stopped about 15 minutes after decapitation.

Animals decapitated several weeks after arousal, or decapitated in a nonhibernating season, showed a temporary *increase* in heart rate during the first minute and a half after decapitation, preceding the usual decrease. This interesting transient increase in rate was not seen in any of the hibernating or arousing corpora immediately following decapitation. If this spurt observed in a season in which an animal is not hibernating is due to the sudden loss of normal vagal tone following decapitation, the inference can be drawn that normal vagal tone was lacking in hibernating or arousing animals in which such an increase in heart rate was not seen following decapitation. In each experiment conducted in a time of the year (summer) in which hibernation is infrequent, the transient increase in rate did occur within a minute or two after decapitation, although in some of these cases the prolonged continuance of heartbeat after such decapitation (continuance of heartbeat such as is seen in, and is characteristic of, a hibernating season) did occur.

The contour of the recorded electrical discharge changed rapidly in the first few minutes after decapitation in hibernating or arousing animals. After a time the QRS complex frequently consisted of a prolonged diphasic wave. As the preparation deteriorated, a notch in the R wave frequently appeared, which became deeper until sometimes the R wave became two entirely separate deflections, suggesting that the ventricles were contracting independently. This was later confirmed visually on isolated hearts. Eventually the left ventricle stopped beating and contraction could be seen only in the right ventricle, with a resultant return to a monophasic electrical discharge. The P wave was distin-

guishable until the reduction in amplitude of the whole deflection became such that it could not be detected. The P-R interval became progressively longer (Dawe and Morrison[4]). The last electrical discharges recorded were very small and monophasic curves which were probably due to slight terminal contractions in the right ventricle. Slow drifting and occasional sudden shifts of the base line were often seen in late stages.

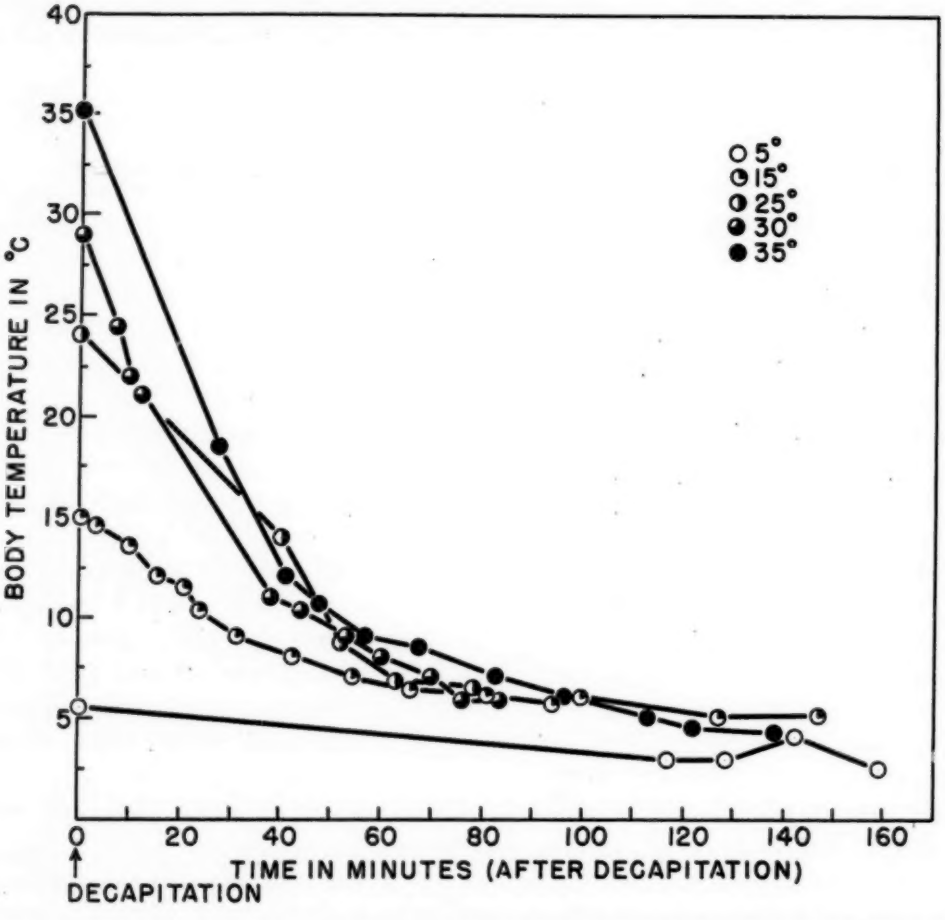

Fig. 1.—Body temperature changes in a cold chamber are compared after the decapitations of five animals. One animal (initial body temperature = 5°C.) was in deep hibernation at the time of decapitation. The other four were progressively more aroused (as defined by the initial body temperature of each).

After decapitation of animals in the summer (in which the chest was opened to observe the beating heart) a rapid development of heart block occurred, followed by ventricular standstill. Atrial contraction continued in some cases for a relatively long period of time thereafter (an hour or more).

The relative work of hibernating or arousing hearts after decapitation may be approximated by the number of beats produced in a given period of time or by the total number of beats following decapitation. This is shown in Fig. 3, for successive 10-minute intervals after decapitation. There is some indication that the hearts of animals decapitated in deep hibernation and the hearts of

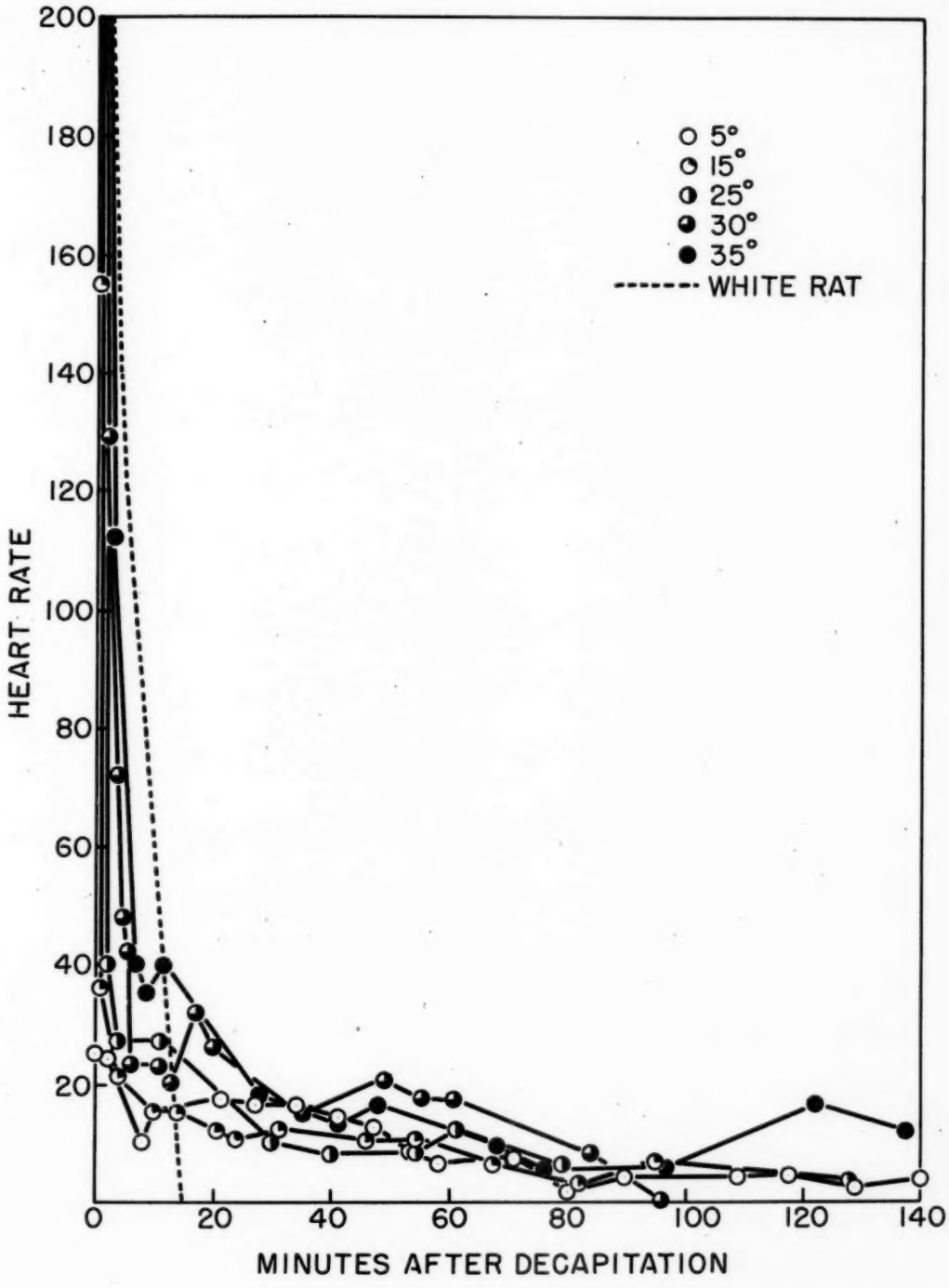

Fig. 2.—Decline in heart rates after decapitation of the same five animals indicated in Fig. 1. It is quickly apparent by comparing Figs. 1 and 2 that change in heart rate is not simply a function of a fall in body temperature, and it is also apparent that all ground squirrel hearts (whether hibernating or arousing) maintain the faculty of extended beating in the cold after decapitation, in contrast to the heart of an animal which does not hibernate (white rat).

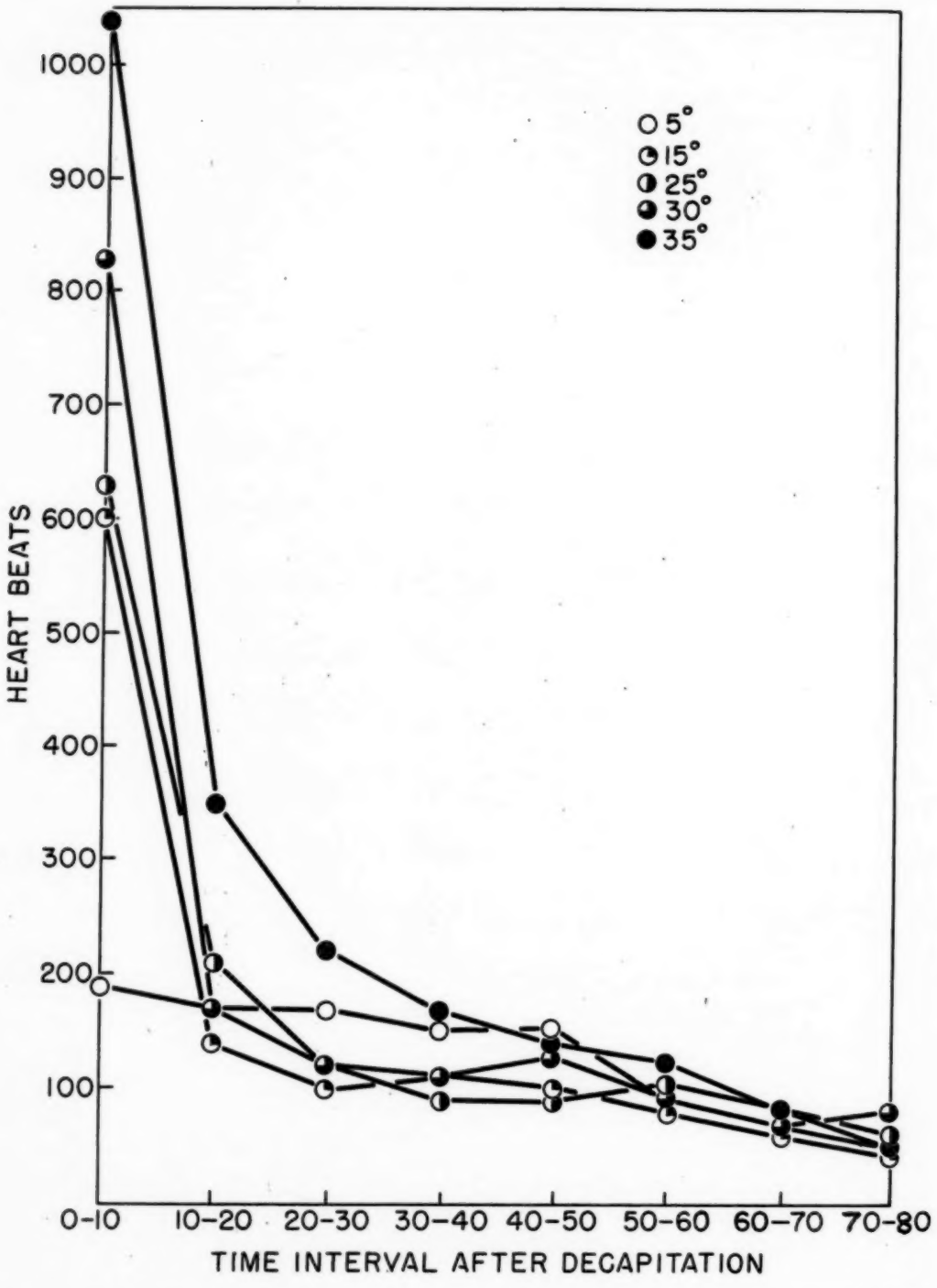

Fig. 3.—Number of heartbeats produced after decapitation by the same five ground squirrels indicated in Figs. 1 and 2. The number of beats produced per unit time after about 20 minutes following decapitation remains fairly constant and is relatively independent of the state of arousal of the animal.

animals decapitated after arousal (T_b = 35°C. or above) have a greater ability to produce beats than do the hearts of animals decapitated in mid-arousal, if one compares the total number of beats produced after decapitation in hibernation, various stages of arousal, and after arousal (Fig. 4). There was some difficulty in determining accurately the time at which all electrical activity ceased in these experiments. However, the heart was beating progressively more slowly, so that a slight error in final count had little effect upon the computation of the total number of beats produced.

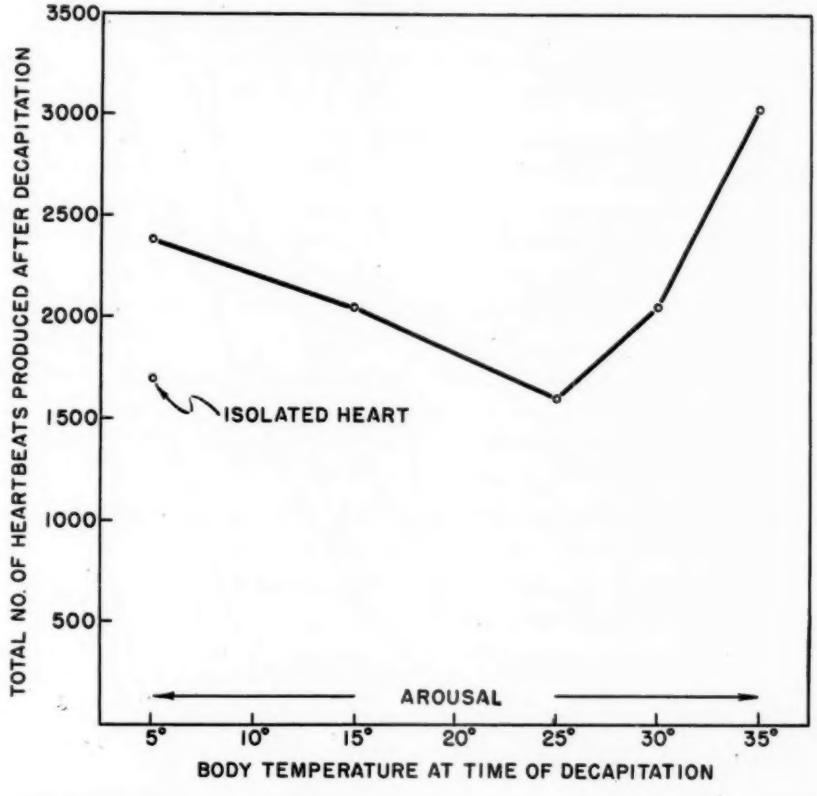

Fig. 4.—Total number of heartbeats produced after decapitation by the same five animals indicated in Figs. 1-3. These total beats are compared to the total beats of an isolated hibernating heart. Following the curve from left to right approximates changes in the viability of the heart through the arousal process.

It was often possible to record rhythmic electrical discharges from the isolated heart from the hibernating ground squirrel for long periods of time. In one experiment (C-98), cardiac activity was detected at intervals for 22.5 hours after isolation. About one hour after isolation, contraction was no longer visible, but electrical activity was recorded for a time. Later, it too disappeared. The heart was then removed from the saline, mechanically stimulated, and placed in fresh cold saline. This restored both visible contraction and electrical activity for a while, but soon mechanical contraction and, later, electrical discharge again disappeared. This heart was successfully revived in this manner six times in the 22.5 hours. In another experiment (C-84), the saline solution containing the

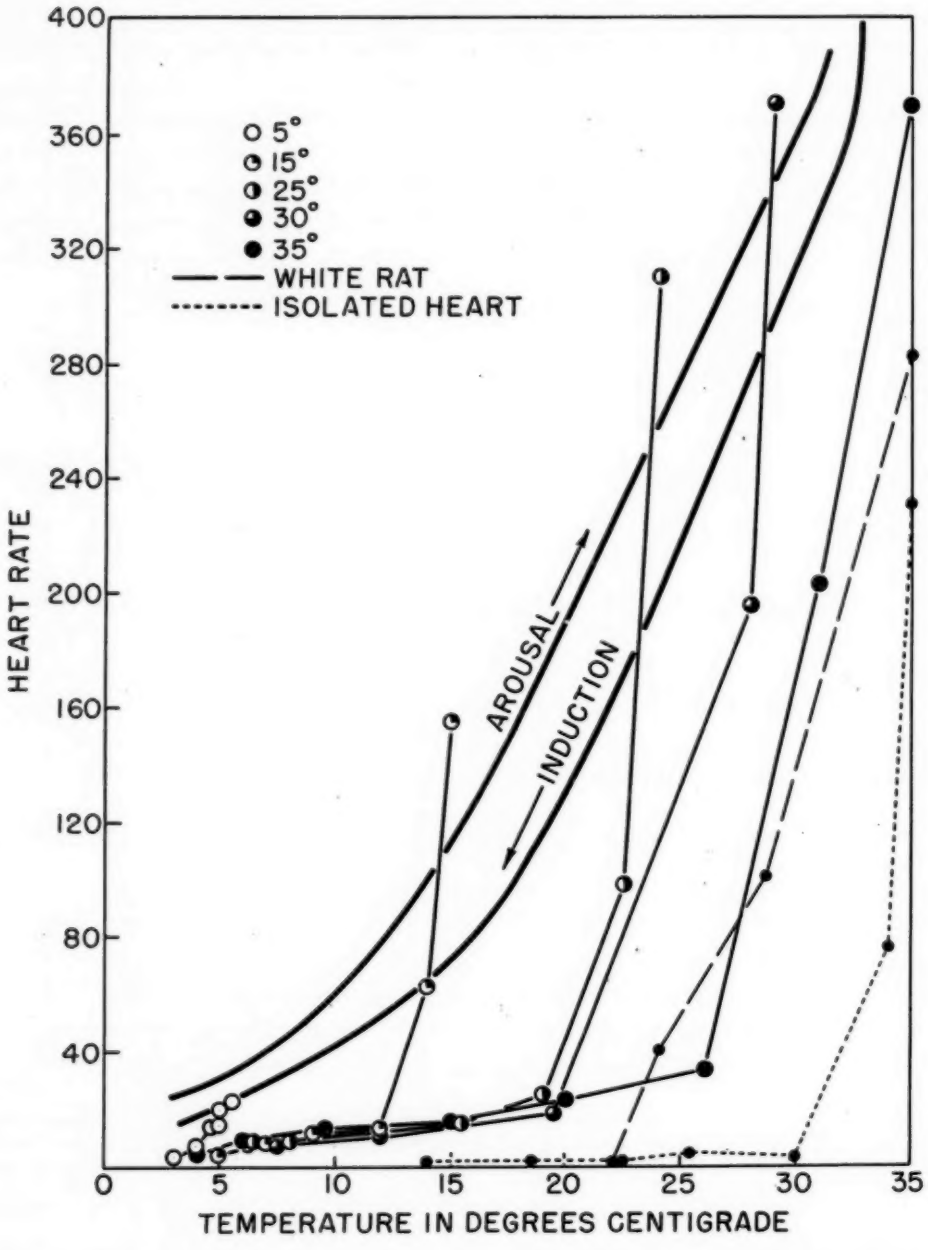

Fig. 5.—First, this graph illustrates (by the heavy black line) the smooth curve showing heart rate in induction and in arousal of the 13-lined ground squirrel. The curve was drawn as a best fit for 101 heart rates taken on ground squirrels undergoing natural induction and as a best fit for 177 heart rates taken on ground squirrels undergoing natural arousal. Second, the graph shows the heart rate as a function of body temperature for the same five decapitated animals described in the preceding figures. Thus, the decapitated animals achieved the low heart rates characteristic of hibernation at body temperatures higher than natural hibernation. However, these hearts stabilized in rate (close to 20 beats per minute) as well as in time (about 20 minutes following decapitation—Fig. 2). Stabilization did not occur as a function of body temperature. The shift from "arousing heart" back to "hibernating heart" is thus apparently related more closely to time and heart rate than it is to body temperature. This is further evidence for the fact that the hibernating heart (or arousing heart) is operative relatively independently of body temperature.

isolated heart was allowed to warm. The heart rate remained relatively constant at about 20 beats per minute until the temperature reached 19°C., at which time visible and electrical activity suddenly stopped. The saline was cooled and electrical activity reappeared at 12°C., but visible contractions were not seen.

In a final case, the isolated hibernating heart was placed directly in 37°C. saline. Visible as well as electrical activity ceased within 2 minutes, but irregular electrical discharges resumed when the saline was cooled below 31°C.

In all of the isolated hibernating heart preparations, rhythmic electrical discharge was obtained for a time after contraction could no longer be detected visually. The contour of the deflection in the isolated heart records was largely dependent upon the position of the heart in relation to the electrodes. Therefore, further interpretation cannot be made of the significance of contour change.

In Fig. 5, heart rate as a function of fore temperature is shown for five decapitated hibernating or arousing ground squirrels, a decapitated white rat, and an isolated ground squirrel hibernating heart. In addition, composite curves of heart rate in many experiments, obtained on many intact ground squirrels during induction and arousal (Landau[5]) are included. After decapitation, the heart rates of hibernators which had been arousing fell rapidly to very low rates, and thereafter decreased at the rate of about one beat per minute per degree of drop in body temperature. The heart of the decapitated white rat, on the other hand, did not make the shift to the low rate. Instead, it decreased progressively in rate to cessation, and showed no signs of mechanical or electrical activity below a body temperature of 22°C. The rate of beating of the isolated heart was much slower than that of the hearts in decapitated animals.

The courses of the initial drops in heart rate were nearly parallel in the animals decapitated at various stages during arousal. This amounted to a decrease of more than 100 beats per minute per degree of drop in temperature in the first 10 minutes, and about 45 beats per minute per degree over the first 20 minutes. This is a much sharper change than occurs in induction in the intact animal (15 beats per minute per degree). By comparing Figs. 1 and 5, it can be shown that the initial rapid decrease in heart rate after decapitation is not related to the rate of body cooling.

DISCUSSION

I. *The Hibernating Heart.*—Characteristics of the heart of the hibernating mammal otherwise not described herein have been described in recent years by several other investigators, notably Suomalainen and Sarajas,[6] Sarajas,[7] and Johansson.[8]

The survival of the isolated hibernating heart in a cold in vitro environment poses questions as to the response of this heart to temperature change. Such a heart must either possess an intrinsic mechanism making possible such beating despite the extreme cold of its "milieu interior," or it must receive such a tremendous stimulus of another order that depression of its automaticity by cold is not effectual to the point that the heartbeat is brought to a standstill.

In the case of the isolated hibernating heart, in which the heart beats in the cold and without connection to the animal body, it seems self-evident that the rationale which could explain such beating is to be found in a study of the heart (musculature) itself. On the other hand, if this faculty for continued beating of the hibernating heart in the cold is destroyed or weakened by isolation, the rationale for continued beating must be sought elsewhere. In view of the fact that continued beating of the isolated hibernating heart is sometimes observed for hours after extirpation, it can be said that as a first approximation it seems to be true that the mechanism for maintenance of the beating of the hibernating mammalian heart in the cold resides in the heart musculature, which must have been changed in some way (either seasonally or phylogenetically) so as to perform this normally unphysiologic action. This phenomenon seems to be in line with the description of "biological zero" for heartbeats which is determined wholly within the heart (Adolph, Klem, and Morrow[9]). If the phenomenon is seasonal, the tissue of the heart of an animal which is capable of hibernating undergoes changes which begin sometime prior to hibernation and progress into the hibernating season or period. (Note: The use of the word "season" in this context is not to be confused with the sense of the word implied in the "four seasons," or the two seasons—winter and summer. The use of the word "season" here refers to a preparatory period—a season, that is, which can be induced at any time of the year. Thus, at the First International Symposium on Natural Mammalian Hibernation at Endicott House, held on May 13-15, 1959, several investigators in addition to the present authors—chiefly, Dr. C. Lyman,[10] of Harvard, and Dr. G. Bartholomew,[11] of the University of California in Los Angeles—described their observations of hibernation occurring in mammals in a summer "season.") A good deal of evidence is at hand for a preparatory period prior to hibernation in which tissues (particularly fat) undergo physical and biochemical change (Lyman,[12] Fawcett and Lyman,[13] South,[14] Strumwasser[15]). These tissue changes probably condition the heart (as an example of a typical hibernating organ) for a situation in which it must remain functional in the cold. Such a preparation which the tissue of the heart may undergo in order to make possible hibernation would have three characteristics: (1) The heart would attain better cold hardihood (it would become better able to survive in the cold). (2) The heart would become relatively temperature-change insensitive. (This may be a restatement of point 1.) Temperature-change insensitivity is noted in the fact that over the hibernating body temperature range the heart rate changes very slightly—seldom more than 1 beat per degree of temperature. (3) The heart would acquire a sensitivity to factors which would make it possible for it to increase its rate tremendously in arousal although cold and in a cold animal body.

The total picture would be that of a heart intrinsically changed from what it was in the period prior to hibernation. This heart would now be cold-hardy. It would be essentially devoid of influences of vagal tone. It would be hyperirritable in the cold and probably responsive to some endogenous stimulus which is not seen in the nonhibernating heart. A duality of enzymatic pathways comes immediately to mind—one pathway serving a high-temperature situation, and a second metabolic system operative in the cold.

II. *The Heart in the Animal Arousing From Hibernation.*—The system which operates at the low body temperature of hibernation can be triggered to speed up tremendously in arousal in an intact animal body. This capability has not been seen in the case of the isolated hibernating heart. Thus, the stress of arousal on this heart must be initiated by intimate connections with the animal body, and as a first probability, since arousal proceeds rapidly, the sympathetic nervous system can be implicated for this function. Lyman and co-workers have pointed to the sympathetico-adrenal system as being primarily implicated in the arousal process (for example, Lyman and Chatfield[16]). In view of the fact that it appears to be true that the vagus has been rendered inoperative, it would seem that the rapid increase in heart rate of arousal is due in part to a return of activity of the cardio-accelerator nerves operating on a "physiologically vagotomized" heart. Secondly, since extrapolations of increases in respiratory rates are noted to begin prior to increase in heart rate (Landau and Dawe[17]), and in view of the noted irritability of the hibernating heart to exogenous mechanical movement, the combination of thoracic movements acting against this heart musculature and restimulation of cardio-accelerators on a cold "physiologically vagotomized" heart must largely contribute to the rapid increase in heart rate in the cold animal body. Thirdly, animals decapitated in various stages of arousal seem to possess a decreasing, followed by an increasing, ability to produce heartbeats as arousal progresses (a stage of arousal is defined, in this respect, by the body temperature of the arousing animal at the time of decapitation). This fact may imply that the metabolic stores of the arousing heart are gradually lost and then recovered, as compared to those of the isolated hibernating heart, if total heartbeat production after decapitation or isolation is used as a criterion. The loss of such metabolic stores may, in fact, represent a greater utilization (than in hibernation) of such stores per heartbeat during the first stages of arousal. The acquisition of ability to produce heartbeats may represent a "restocking" of metabolic stores as arousal proceeds to completion.

III. *The Heart in an Animal Inducing Hibernation.*—The cooling curve of a critically Nembutalized nonhibernating ground squirrel approximates that of the natural state in a ground squirrel beginning (inducing) hibernation down to a body temperature of about 20°C. It seems that the first step in induction is very much like Nembutal anesthesia, insofar as the heart follows a cooling curve similar to that in Nembutal anesthesia. However, at a critical juncture, the heart which is about to hibernate no longer continues to slow (to termination of beat as in the critically Nembutalized animal) but, rather, maintains an extremely slow rate at an essentially unchanging frequency. In other words, it is *stimulated* to continue to beat. It may be that this is a response to a "physiological vagotomy"; but it is very improbable that cardio-accelerator stimulation is responsible, since this heart will continue this beating in isolation. Low-level cardio-accelerator activity may be present, insofar as some difference in survival in favor of the heart of the decapitated hibernating animal is seen, as compared to the isolated hibernating heart. It is obvious that nervous disconnection of the heart from the body is not the whole story in explaining continuance of heartbeat, since this hibernating heart continues to beat in isolation in the cold in contrast to other

mammalian hearts. In other words, the achievement of a maintenance system for the continuance of beating must be a function of the heart musculature itself, and it would seem to have two characteristics—a *preparatory* characteristic and a cold *maintenance* characteristic. The former could represent a hormonal change which is noted in the remarkable changes in endocrine glands in the prehibernatory season (Foster, Foster, and Meyer,[18] Kayser,[19] Deane and Lyman[20]), and the latter could represent an enzymatic shift within the cardiac musculature.

IV. *The Hibernating Heart of the Warm-Blooded Mammal vs. the Heart of the Cold-Blooded Chordate.*—It can be readily noted that the hibernating mammalian heart behaves in the cold and in isolation like a cold-blooded (poikilothermic) heart, for example, that of the frog or turtle. However, the heart of the mammal which hibernates exhibits this phenomenon in isolation as a pronounced physiologic change from other mammals and only consistently at times of hibernation. This change in the mammal to a "hibernating heart" is a more radical change than is the annual conversion of an amphibian heart from the "summer heart" to the "winter heart" condition (Smith[21]).

SUMMARY

Decapitation during hibernation and observation of the beating heart, or observation of the isolated heart of the hibernating thirteen-lined ground squirrel displayed survival of this heart in the cold for periods of time far in excess of that seen in nonhibernating mammals (the rat) subjected to the same experimental methods. This phenomenon has been studied and data have been collected, about which speculation is made and which is summarized as follows:

1. *Heart in hibernation:* A hibernating heart is relatively temperature-insensitive throughout the range of hibernating temperatures (0° to 20°C.). Contrarily, it is very sensitive to tactile stimulation. The mechanical contractions of an isolated hibernating heart may be extremely faint (to a point at which they cannot be observed visually), whereas electrical beating may continue for hours after visible contractions are no longer observable. This latter property poses the question whether in the intact hibernating mammal the heart actually moves blood with each electrical record of a heartbeat.

2. *Heart in arousal from hibernation:* Stimulation to initiation of arousal of the hibernating heart is triggered by the action of a sympathetico-adrenal mechanism on a "physiologically vagotomized" heart. Initiation of arousal is further strengthened by respiratory muscle contractions in proximity to the heart at rates which act as "pacemaker" for the entire arousal process. Thus, the early arousal process of the heart seems to be geared to nervous and mechanical mechanisms, but not to a change in body temperature. Later in the arousal process, further stimulation of the heart rate is certainly modified in the direction of still further increases in rate by a rise in body temperature. There is evidence for changes in metabolic stores within the heart musculature as arousal proceeds.

3. *Heart in induction to hibernation:* The stimulus to induction of the heart into hibernation seems to have four elements: (a) a preparatory phase (possibly hormonal) during which the musculature of the heart is readied (this may be "sea-

sonal," in the sense that the animal "readies itself," not in the sense of the "four seasons"); (b) a fall in body temperature during which the heart rate of the animal entering hibernation follows a cooling curve similar to that in Nembutal anesthesia plus cold for such an animal; (c) a "physiological vagotomy" with possible maintenance of sympathetico-adrenal stimulation at a very low level; and (d) a shift from one metabolic scheme to another (probably enzymatic) when the body temperatures falls below 20°C.

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The Prospects for Direct-Writing Phonocardiography; With a Short Critique of Spectrophonocardiography

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Direct-writing techniques possess certain distinct advantages in the registration of electrocardiograms, intracavitary pressures, etc. Apart from the elimination of photographic processing, inspection of the directly inscribed record usually indicates promptly whether the apparatus is functioning satisfactorily, and frequently suggests the necessary corrective measures in the event of malfunction. A reliable, direct-writing phonocardiograph should provide similar advantages.

We report here a pilot clinical evaluation of a direct-writing phonocardiograph which was assembled from currently available components. The results of this study show striking promise, even though the dynamic capacities of the equipment were not designed for the application to which we put them. By extrapolation from the pilot study, however, we believe that it is feasible to develop a direct-writing phonocardiograph of good diagnostic quality.

In the course of our design considerations we encountered certain properties of sonic vibrations which have a direct bearing on the spectrum analysis of heart sounds. These properties are described in some detail later in the present report, and are developed into a brief critique of spectrophonocardiography.

METHODS AND RESULTS

The components employed in the pilot evaluation consisted of a dynamic type of heart microphone,* a phonocardiographic amplifier,† and a single-channel, direct-writing electrocardiograph.‡ The output of the microphone was fed to the input of the phonoamplifier. An "audiophone" outlet of the phonoamplifier was loaded with a 120-ohm resistor, and then coupled through a high-pass filter to one input grid of the electrocardiograph. The other input grid was electrically grounded. The high-pass filter consisted of a simple RC network such as was recently described

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*Model 62-1500, Sanborn Company, Waltham, Mass.

†Model 62-500, Sanborn Company, Waltham, Mass.

‡Model EK-3, Burdick Corporation, Milton, Wis.

in the clinical literature by Zalter, Hodara, and Luisada.[1] This coupling network was composed of a 1-microfarad capacitor and a resistor which was tapped so as to permit the RC time constant of the filter to be varied in five equal steps from 0.0015 to 0.009 second. With the time constant of the network set at 0.009 second, its high-pass characteristics compensated for the high-frequency attenuation of the electrocardiograph in such a way that the over-all amplitude response of the recorder was virtually uniform from 20 to 300 cycles per second. This particular filter setting, then, corresponded to "stethoscopic" registration.[2] Setting the time constant at smaller values produced attenuation of the lower frequencies, thus approximating "logarithmic" registration.[2]

The apparatus assembly was tested by a series of simultaneously recorded direct and photographic phonocardiograms obtained from normal and abnormal subjects. In numerous trials the tracings compared rather favorably with each other, but in some instances the directly inscribed phonocardiogram was decidedly inferior to the photographic record.

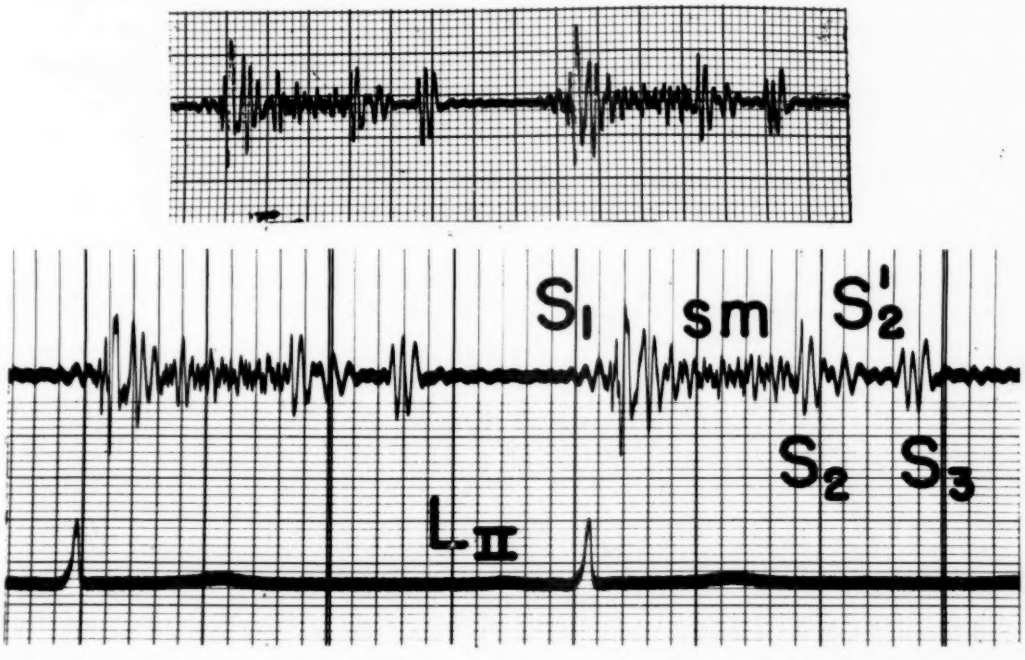

Fig. 1.—Heart sounds recorded from the apical region of a patient by means of a direct-writing technique (upper tracing; 50 mm./sec.). The lower tracing (75 mm./sec.) is a simultaneously recorded optical tracing, together with Lead II of the electrocardiogram. Further description in the text.

Fig. 1 shows a typical favorable result, recorded from the apical region of a patient with mitral insufficiency. This illustration shows that the major vibrations of the first sound (S_1), a split second sound (S_2 and S'_2), and a third sound (S_3) recorded by the direct technique resemble very closely those of the photographic tracing. In addition, the systolic murmur (sm) is readily distinguishable in the direct tracing, and its relative amplitude is approximately the same as that displayed in the optically recorded tracing. On the other hand, the fine splintering and notching of both the murmur and the major vibrations tend to be erased by the direct method of registration.

In general, the direct technique provided reasonably satisfactory stethoscopic registration of normal heart sounds, and of coarse, relatively low-pitched murmurs such as that illustrated in Fig. 1. However, in the case of higher pitched, blowing murmurs the recording system exhibited inadequate amplitude and form response to the higher sound frequencies. Some augmentation of the higher frequency components could be produced by switching the compensating network to a smaller time constant, but this maneuver caused the vibrations to "ride a hump" rather than to oscillate about a fixed base line. We conclude from the clinical trials that the instrument

assembly described here is not generally acceptable for diagnostic phonocardiography because of its limited and/or distorted response to the high-frequency components of heart sounds. As will be shown, however, it is possible, in principle, to greatly minimize these limitations by means of relatively simple modifications of the recording apparatus.

REQUIREMENTS FOR ADEQUATE PERFORMANCE

Although the galvanometer which we employed appears to be quite acceptable for its intended purpose of conventional electrocardiographic registration, a recorder of superior dynamic characteristics is required to meet the more stringent demands of reliable phonocardiographic registration. Consequently, we encountered certain technical deficiencies in our clinical testing program which, as exemplified by Fig. 2, could not be entirely circumvented by the "brute-force" method of electronically boosting high-frequency response. The figure shows

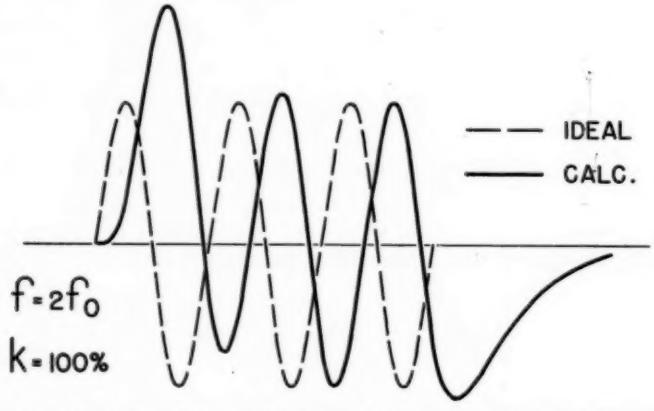

Fig. 2.—Illustration of artefacts inherent in the "brute-force" method of driving a critically damped galvanometer. The idealized oscillations are assumed to have a frequency of 75 c.p.s., as compared to a galvanometer f_0 of 37.5 c.p.s. Further discussion in the text.

the response of a critically damped galvanometer to a three-cycle burst of sinusoidal vibrations which have a frequency of twice the undamped natural frequency of the galvanometer. Because of dynamic transient effects the initial galvanometer response overshoots the amplitude of the ideal response by approximately 67 per cent. As the transient effects fade, the steady-state response is observed to lag approximately three eighths of a cycle behind the ideal response. For driving forces of still higher frequencies the initial overshoot effect is progressively exaggerated, and may override the first several response cycles. This explains in part why the higher frequency vibrations of our phonocardiograms seem to "ride a hump." The other reason for such behavior is overloading of the power amplifier.

The conventional direct-writing galvanometer is an electromagnetic-mechanical type of transducer, the fundamental dynamic characteristics of which are well known.* The manner and degree in which the dynamic limitations of

*E.g., see Reddick and Miller,[3] pp. 74-81; Gilbert,[4] pp. 197-202. Pertinent equations, abstracted from these sources, are given in the appendix.

the instrument are exceeded determine the nature and magnitude of the distortion which it produces. Two parameters of paramount importance govern galvanometer design. The first is the natural, undamped frequency (f_0), the frequency at which the galvanometer would resonate if there were no drag upon its movements. The second parameter is the dragging force upon galvanometer movements, and is usually expressed as a damping coefficient, k. For values of k greater than zero and less than unity, free oscillations of the galvanometer can occur, which decay exponentially (*underdamped* state). The galvanometer is just aperiodic for a damping coefficient of unity (*critically* damped). Coefficients greater than unity *overdamp* the galvanometer and are to be avoided. On the basis of the two parameters, f_0 and k, the following types of distortion can be analyzed and minimized: phase lag, distortion due to transients, distortion due to harmonic content, and power requirements.

Phase Lag.—Recording galvanometers possessing significant inertia inevitably lag behind the driving forces which are applied to them. The lag is exactly one quarter-cycle when a sinusoidal driving force of frequency, f_0, is applied to the galvanometer. The lag diminishes progressively for driving frequencies of less than f_0, and increases for driving frequencies greater than f_0. The lag never exceeds one half-cycle. Reducing the damping coefficient minimizes lags of less than a quarter-cycle, and increases lags of more than a quarter-cycle. According to these relationships the f_0 of the system should be as great as possible, and the damping coefficient as small as is compatible with other considerations. Although the latter condition exaggerates the phase lag of relatively rapid vibrations, they will never be delayed by more than a half-cycle.

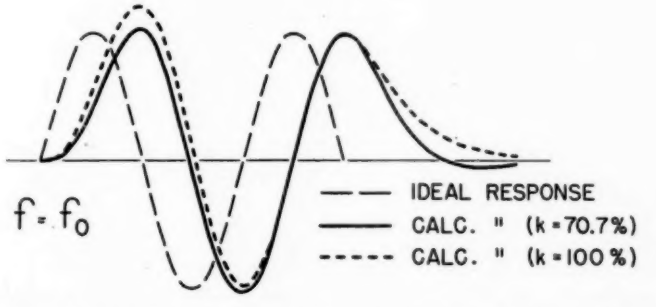

Fig. 3.—Reduction in registration artefacts by improvement in galvanometer design. As in Fig. 2, the idealized oscillations are assumed to have a frequency of 75 c.p.s. The galvanometer f_0 has been increased to 75 c.p.s., and the damping coefficient reduced to 70.7 per cent of critical (solid curve). The improved galvanometer characteristics reduce the artefacts shown in Fig. 2, but less so if critical damping is retained (short-dashed response curve). Further discussion in the text.

Distortion due to Transients.—Abrupt onset and offset of sonic energy produces the type of distortion shown in Fig. 2. In order to minimize this type of effect the f_0 of the galvanometer should be at least equal to the driving frequency, and greater if possible. The damping factor is also of considerable importance. If it is greater than necessary, it will exaggerate the transients of the system. If it is too small, the transient response becomes a decaying oscillatory movement which is superimposed on the recorded wave form. As shown in Fig. 3, a damping

coefficient of 70.7 per cent of critical is a reasonably good compromise.* For this degree of damping the free oscillations of the system decay at the rate of 95.7 per cent per half-cycle. A damping factor as low as 65 per cent of critical would probably be acceptable.

Distortion due to Harmonic Content.—Nonsinusoidal types of periodic sonic energy may be represented as the sum of several sinusoidal components whose frequencies are exact multiples of the fundamental frequency. Distorted registration occurs because the phase lag is different for each component. Furthermore, sudden inflections in wave form bespeak a high-frequency content which is beyond the response capability of the instrument.

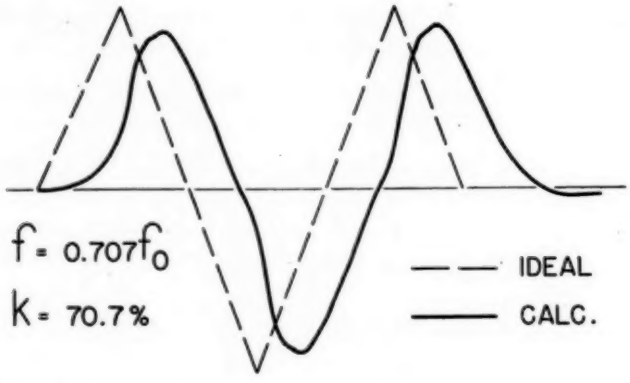

Fig. 4.—Illustration of artefacts due to distorted registration of harmonics. The galvanometer is assumed to have an f_0 of 100 c.p.s., and a k of 70.7 per cent. The idealized, triangular deflections, which have a frequency of 70.7 c.p.s., impose greater dynamic stresses upon the recording system than the stresses imposed by actual heart sounds of comparable frequency.

An example of distortion due to harmonic content is shown in Fig. 4. The driving force consists of a one and one half-cycle burst of sonic energy in the form of isosceles triangular spikes. The f_0 of the galvanometer exceeds the fundamental frequency by 41.4 per cent, and its damping coefficient is 70.7 per cent of critical. The steady-state response of the galvanometer is assumed to be uniform for frequencies up to nine times the fundamental frequency, and then to fall off sharply. The loss of the sharp peaks in the calculated wave form is due largely to the inability of the galvanometer to respond to frequencies beyond the ninth harmonic. An alternative interpretation is that sharp peaks represent instants of infinitely great acceleration, which in practical applications exceed the power capabilities of the amplifier and galvanometer. The peculiar inflections in the response curve result from the different degree of phase lag of the various components.

Power Requirements.—As the f_0 of the recording device is increased by stiffening its mechanical suspension, the power requirement increases proportionally to the fourth power of f_0. The recorder employed in this study had an f_0 of 35.7 cycles per second, and required 157 milliwatts of direct-current energization to

*This conclusion is at variance with that of Orias and Braun-Menendez,[5] who recommend the use of a fully damped recorder.

produce a steady deflection of 1.0 cm. The damping coefficient due to mechanical friction alone was less than 6.2 per cent of critical. Assuming a peak-to-peak response of 1.0 cm. and a total damping coefficient of 70.7 per cent, we calculated the power versus the frequency characteristics (Fig. 5) of the galvanometer when its suspension was stiffened sufficiently to produce f_0's of 37.5, 75, and 150 cycles per second, respectively.

Fig. 5 illustrates another basic defect in the brute-force method of amplitude compensation. In all three cases the power requirement is negligible at resonant frequency, but in the first two cases it rises quite steeply as frequency increases, and soon exceeds the power curve for $f_0 = 150$. Assuming that the galvanometer coil is capable of dissipating heat at a peak rate of 10 watts, the instrument is capable of covering a frequency range of near-zero to 225 cycles per second when the suspension is stiffened sufficiently to increase f_0 to 150. The peak value of 10 watts is probably realistic since a steady full-scale deflection requires 1 watt.

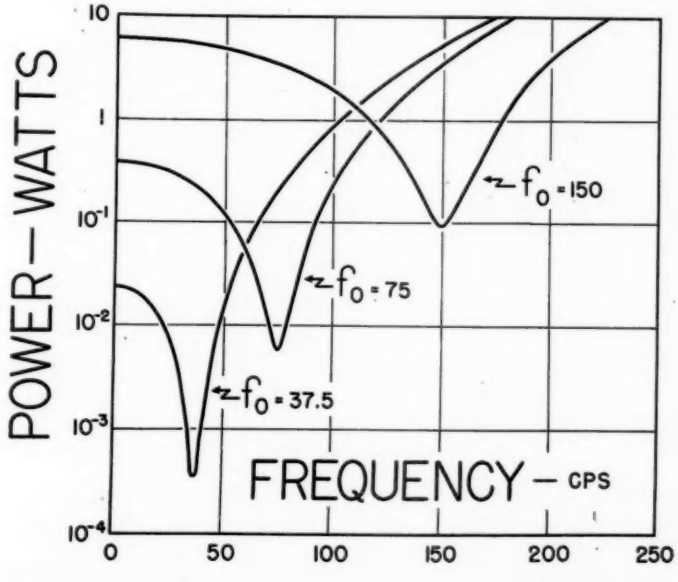

Fig. 5.—Power requirements of a conventional direct-writing galvanometer for degrees of suspension stiffening which increase its f_0 to 37.5, 75.0, and 150 c.p.s., respectively; calculated for a peak-to-peak amplitude of 1 cm. Optimal shortening of the stylus would reduce these power requirements by one half. Further discussion in the text.

Because phonocardiograms with peak-to-peak amplitudes of approximately 1 cm. are satisfactory, it is feasible to employ a shorter writing arm. Herein lies another means for improved performance, since most of the moment of inertia in the galvanometer which we tested was due to the stylus. Assuming that the stylus mass per unit length remains unaltered, we calculate optimal stylus shortening to be 43.3 per cent of its original length. This procedure reduces by one half the amount of power required to duplicate the performance characteristics shown in Fig. 5. Conversely, the same amount of power employed under this condition of increased efficiency stretches out the power-frequency curves by 18.9 per cent along the horizontal axis of the figure.

THE INFLUENCE OF VARIABLE FREQUENCIES ON THE SPECTRUM ANALYSIS OF HEART SOUNDS

The idealized variable-frequency vibrations illustrated in Fig. 6 and repeated in the top of Fig. 7 show the first five cycles (from zero time) of the oscillatory function, $y = \sin (200 \pi t + 3 \sin 20 \pi t)$, where y is the amplitude of deflection, and t is time in seconds. The function can be thrown into series form, and is expressed to four-place accuracy by

$$y = \sum_{n=3}^{n=17} J_{n-10}(3) \sin 20 \pi n t,$$

where the n's are positive integers; and the J's are the first kind of Bessel functions of argument, *3*, and order, $n - 10$.[3,6]

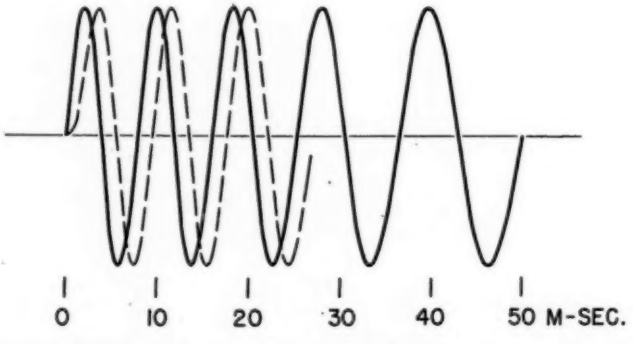

Fig. 6.—Response of a direct-writing galvanometer (dashed curve) to phase-modulated vibrations (solid curve) which vary in frequency from 130 c.p.s. at the onset, to 70 c.p.s. at 0.05 second. The dynamic parameters of the recorder are f_0 = 150 c.p.s., and k = 70.7 per cent. Following the initial transient period, the response is excellent except for phase lag.

The series form signifies that the variable-frequency function is equivalent to the sum of numerous simple harmonic components of known frequency and amplitude. In the particular example illustrated by Fig. 7 the harmonic components are: Carrier—100 cycles per second (median frequency), amplitude 26.0 per cent of the variable-frequency oscillations. First pair of side-band frequencies—90 and 110 c.p.s., amplitude 33.9 per cent. Second pair of side-band frequencies—80 and 120 c.p.s., amplitude 48.6 per cent. Third pair of side-band frequencies—70 and 130 c.p.s., amplitude 30.9 per cent. Fourth pair of side-band frequencies—60 and 140 c.p.s., amplitude 13.2 per cent. Fifth pair of side-band frequencies—50 and 150 c.p.s., amplitude 4.3 per cent; and so on, with rapidly decreasing order of amplitude. The carrier oscillations and the first five pairs of side-band frequencies are depicted graphically in Fig. 7.

Spectrum analysis of the idealized variable-frequency vibrations with presently available techniques[7] would produce a columnar pattern composed of equally and closely spaced horizontal streaks. Each of these streaks would correspond to a given harmonic component of the vibrations, with the ordinate and

density of each streak indicating the frequency and amplitude of the component, respectively. The density of the streaks would be fairly uniform between the levels of 70 to 130 c.p.s., except for some lightening at 100 c.p.s. The density of the streaks would be appreciably lighter at the levels of 60 and 140 c.p.s., and would decrease rapidly above and below these two frequencies. Assuming that the apparatus did not suffer appreciably from lag and ringing, the density of the pattern at each frequency level would be uniform throughout the entire 0.05-second interval occupied by the vibrations.

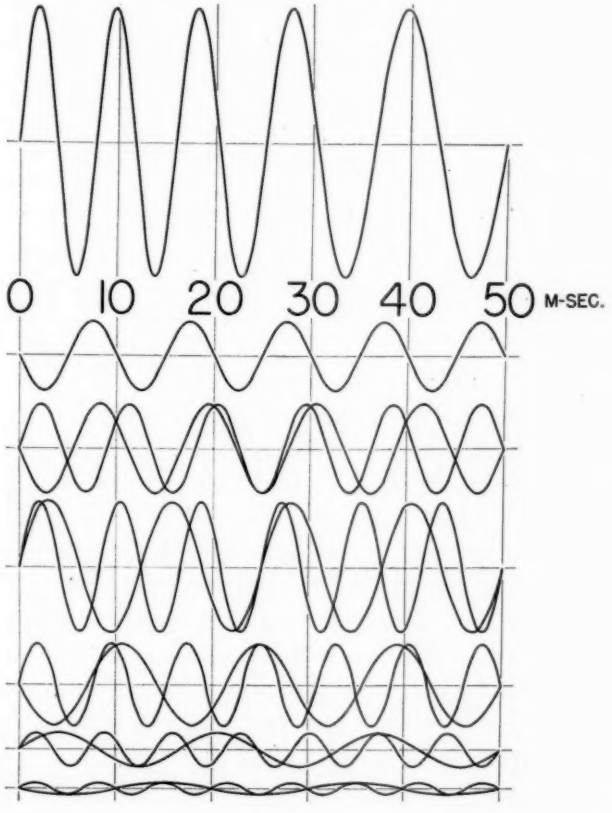

Fig. 7.—Illustration of the simple harmonic components of the phase-modulated vibrations which are depicted in the top strip of the figure. Reading from top to bottom, the succeeding strips depict, respectively, the amplitude and frequency of the carrier, the first pair of side-band frequencies, the second pair of side-band frequencies, etc. The nature of the harmonic components is described more fully in the text, and their presumptive relation to spectrum analysis of heart sounds is presented.

This hypothetical pattern illustrates what we believe to be a fundamental shortcoming of spectrophonocardiography in so far as the registration and analysis of nonmusical heart sounds are concerned. Although the actual vibration frequency changes progressively from 130 to 70 c.p.s. during a 0.05-second time interval, the spectrum analysis displays the entire gamut of these and other frequencies occurring uniformly throughout the entire interval. Furthermore, the spectral pattern is no different for any other time-segment of the function; not even for complete reversal of the order of frequency changes.

Two particularly illuminating examples of potential limitations in the spectrum analysis of heart sounds are provided when the preceding example is so modified that the total frequency range is (a) 124 to 76 c.p.s., and (b) 138.3 to 61.7 c.p.s. In case *a* the 100-c.p.s. component would be lacking from the spectrum; and in case *b* the 90 and 110-c.p.s. components would be absent. Superficial interpretation of such spectra could lead to the erroneous conclusion that the sonic generator did not at any instant oscillate at the frequency of the missing spectral components.

If the dynamic consequences of valve closure were as simple as those initiated by striking a circular drumhead, frequency analysis of the resulting sound would undoubtedly yield a great deal of information regarding the modes of vibrations. Unfortunately, the dynamics of the valve leaflets differ from the simple drumhead model in these important respects: (1) the geometrical configuration is relatively irregular; (2) vibratory movements are heavily damped; (3) damping may not necessarily be a linear function of vibratory velocity; (4) the restorative forces are probably not a linear function of displacement*; (5) the membrane tension is a time-variable function. Items 3, 4, and especially 5 lead to the generation of variable-frequency vibrations. The first equation and its accompanying illustrations exemplify relatively simple frequency variations related to item 5.

In addition to the factors listed above, it is likely that superimposed vibrations occur which are due to oscillations of the chordae tendineae and ventricular walls in the case of A-V valve closure, and of the walls of the great vessels in the case of semilunar valve closure. In short, the dynamics of valve closure sounds must be quite complicated, and this conclusion is supported by the wide spread of frequencies displayed in the spectrophonocardiogram. On the other hand, these same patterns (at least to us) are virtually indistinguishable from random-noise patterns. Therefore we believe spectrum analysis to be of some merit in the consideration of valve closure sounds, but our present feeling is that conventional phonocardiography yields a much more definitive type of information regarding the instantaneous frequency and amplitude of such heart sounds, and consequently provides better insight into the dynamics of the sonic generator.

DISCUSSION

Our design considerations indicate that simple modifications of presently available direct-writing galvanometers can produce a device which is capable of responding to frequencies of more than 250 cycles per second without clinically significant phase lag or transient effect. The fundamental vibration frequency of normal heart sounds and coarse murmurs is ordinarily 100 cycles per second or less. These fundamental frequencies, and at least one additional harmonic component, would be accurately recorded except for relative phase shift. Only the fundamental component of frequencies in the range of 135 to 270 cycles per second would be recorded. Sharp notching and splintering of the wave forms

*Cf., King and Lawton.[5]

would tend to be slurred and smoothed out. None of these defects are considered to be especially objectionable, since ordinary phonocardiographic diagnosis, at least at present, depends largely on the fundamental frequency and temporal interrelations of the sonic vibrations.

Musical murmurs with a fundamental frequency of 270 cycles per second or less would be recorded. Since the onset and offset of such murmurs tend to be gradual rather than abrupt, a significant degree of transient distortion would not be expected. The inability to record fundamental musical frequencies in excess of 270 cycles per second is probably of little practical moment.

In some respects the idealized examples of phonocardiographic response treated here are not especially demanding because of their simple sinusoidal form. On the other hand, the abrupt onset of the hypothetical vibrations, representing an instant of infinitely great acceleration, imposes extremely severe demands upon the dynamic capabilities of the recording device. Accordingly, it is during the initial transient period that the greatest distortion occurs, following which the reproduction is entirely faithful except for phase lag and the relatively unimportant terminal transient.

However, even discounting slurring and notching, valve closure tends to produce a burst of variable rather than fixed-frequency vibrations. Therefore, the five cycles of variable-frequency oscillations shown in Fig. 6 probably represent a valve closure sound more realistically than do simple harmonic oscillations. In contrast to the case of abrupt accelerations and decelerations, Fig. 6 shows that the proposed phonocardiograph should be quite capable of faithfully reproducing sounds whose frequency changes in a relatively gradual manner.

Further analysis of the idealized wave train (Fig. 7) suggests that spectrophonocardiograms of nonmusical heart sounds may be seriously limited in their fundamental significance because of frequency variations.

SUMMARY

The prospects for clinically acceptable, direct-writing phonocardiography have been examined, and found to be favorable.

A pilot clinical study with presently available equipment has been pursued. Although the dynamic parameters of the galvanometer were not designed for phonocardiographic registration, the quality of the tracings was surprisingly good in many instances.

Analysis of the design requirements of direct-writing phonocardiography indicates that relatively simple modifications of existing equipment can raise performance characteristics to a generally satisfactory level, and thus make the advantages of a direct-writing technique available for routine clinical use.

The physical characteristics of variable-frequency vibrations are analyzed in some detail, and are found to have an interesting and important bearing on the significance of spectrophonocardiography.

The authors are pleased to acknowledge the generous loan by the Burdick Corporation of the direct-writer which was employed in this study.

APPENDIX

As stated in the text, phase lag depends upon both the undamped, natural frequency and the damping coefficient of the recorder. The exact relationship is given as the equation,

$$\tan \epsilon = 2kff_\circ/(f^2 - f_\circ^2),$$

where ϵ is the phase angle, and the other symbols have the meaning given in the text.

The steady-state response of the recorder, without frequency compensation, to a sinusoidal driving force is given by the equation,

$$y_p = bf_\circ^2 / \sqrt{(f_\circ^2 - f^2)^2 + (2kf_\circ f)^2},$$

where b is a constant, and y_p is the peak amplitude of deflection at the given frequency.

The transient response in the underdamped case is given by the equation,

$$y = c_1 e^{-2\pi kf_\circ t} \sin (2\pi \sqrt{1 - k^2} f_\circ t + c_2),$$

where e is the natural logarithmic base; t is time in seconds; and c_1 and c_2 are constants which depend upon both the initial conditions and the steady-state response.

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Cardiac Pathology in Experimental Brucellosis

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INTRODUCTION AND BACKGROUND

Evidence that Brucella infection may cause some of the cardiac disease generally assumed to be of "rheumatic" origin has been presented over the years. The evidence may be classified into four categories: (1) clinical evidence in man, (2) pathologic evidence in man, (3) dermal sensitivity to Brucellergen in patients with cardiovascular disease, and (4) cardiac lesions in experimental brucellosis.

The evidence derived from the first three categories is only briefly reviewed, but the study of cardiac pathology in guinea pigs with experimental brucellosis is reported in detail.

Clinical evidence for possible cardiac disease resulting from brucellosis has appeared in the literature ever since the disease was first recognized. The first account of Malta fever was published by Marston[1] in 1861, and subsequently, many workers have pointed to the similarity of brucellosis (undulant fever) to rheumatism and to rheumatic fever. Both Bruce,[2] after whom Brucella and brucellosis were named, and Hughes,[3] who suggested that the disease be designated "undulant fever," made reference to the rheumatic nature of brucellosis.

Pathologic evidence linking cardiac disease in man with brucellosis has been reported not infrequently. The literature records numerous cases of brucellosis involving the endocardium, myocardium, pericardium, cardiac valves, and smaller cardiac arteries (Carpenter and Boak[4]; Spink and Nelson[5]; Rennie and Young[6]; DeGowin, Carter and Borts[7]; Beebe and Meneely[8]; Call, Baggenstoss and Merritt[9]). Whether the cardiac disease was the result of a primary infection with Brucella or was secondary to rheumatic heart disease was frequently questioned. Call, Baggenstoss and Merritt[9] reported in detail two cases of endocarditis due to Brucella. Besides involvement of the aortic valve in one case and the mitral valve in the second, the authors described granulomatous lesions of the auricle and myocardium. They also observed necrotizing arteritis in one case. The author's comment: "It is interesting to note that the myocardial, renal

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and vascular lesions in these cases have certain similarities to those of rheumatic fever, subacute bacterial endocarditis due to green producing streptococci and periarteritis nodosa. . . . Typical Aschoff bodies were not present in either of the cases and the diagnosis of active rheumatic fever was not considered." If the interpretation of the lesions in this report was correct, the two cases of Call, Baggenstoss, and Merritt[9] can be accepted as probable evidence of primary heart involvement in brucellosis.

Recently, Peery[10] has raised the question whether rheumatic fever is the only febrile illness which may cause chronic valvular disease, and whether rheumatic fever is actually a disease entity. He states that, with the possible exception of chorea, all of the five major and seven minor manifestations of rheumatic fever set forth by Jones[11] can occur in brucellosis. Among the five major manifestations of rheumatic fever, Peery refers to carditis especially and states that, although it is not generally known, cardiac involvement in some degree is not rare in brucellosis. Peery and Evans[12] also believe that the electrocardiographic changes almost constantly observed in active brucellosis and chronic valvular disease may be a sequel of nonfatal brucellosis.

A recent study of dermal sensitivity to Brucellergen was carried out by Carpenter and Leik[13] in a hospital population at the Long Beach Veterans Administration Hospital. Among 1,345 male patients tested, 385, or 28.6 per cent, reacted positively. A review of the patients exhibiting a positive reaction revealed that dermal sensitivity to Brucellergen was more prevalent among patients hospitalized for cardiovascular disease than for other types of illness. Thus, a second group of 206 cardiac patients was similarly tested, and 117, or 56.8 per cent, of the group were positive, indicating a past or present infection with Brucella. Sixty-eight cases were diagnosed clinically as having rheumatic heart disease, and 41, or 60.3 per cent, had positive skin tests. The significance of this marked prevalence of dermal sensitivity to Brucellergen among patients with cardiovascular disease is difficult to assess and more data are required. Yet such evidence suggests that Brucella may bear some etiological relationship to morbidity from heart disease.

EXPERIMENTAL BRUCELLOSIS AND HEART DISEASE

Because of the suggestive evidence of cardiac involvement in certain patients with active or chronic brucellosis, a study of cardiac disease in experimental brucellosis in guinea pigs was undertaken. Excluding secondary infection, it may be reasonably assumed that any pathologic changes in the hearts of such guinea pigs were the result of infection with Brucella.

Forty guinea pigs weighing from 250 to 300 grams were injected intraperitoneally with 3×10^7 smooth cells of *Brucella suis*, suspended in 0.85 per cent physiologic salt solution. In addition, 10 guinea pigs were similarly inoculated with *Brucella abortus*–strain 19 employed in calfhood vaccination for Bang's disease in cattle. A third group of 10 animals was observed as uninfected controls and were normal with the exception of one or two cardiac punctures prior to autopsy to determine the effect of such trauma on the myocardium.

The guinea pigs infected with *Brucella suis* were sacrificed from 39 to 383 days after inoculation. One guinea pig, No. 158, the offspring of a mother infected with *Brucella suis* was sacrificed

6 days after birth. Prior to postmortem examination, an intradermal test with 0.2 ml. Brucellergen was carried out. At autopsy, bacteriologic and serologic examinations were made to determine the presence of infection. The heart, together with portions of the lung, liver, spleen, kidneys, adrenal and any other grossly abnormal tissues were removed and fixed in 10 per cent formalin. After fixation, sections from the heart were made at three levels, i.e., at the junction of the great vessels, at the auriculo-ventricular junction, and at the mid-ventricular area. Slides were prepared from the cardiac tissue, stained with hematoxylin and eosin, and examined microscopically. Similar observations were made on the normal guinea pigs and on those infected with *Brucella abortus*–strain 19. This report includes pathologic studies on 37 guinea pigs, 32 inoculated with *Brucella suis* and 5 with *Brucella abortus*–strain 19.

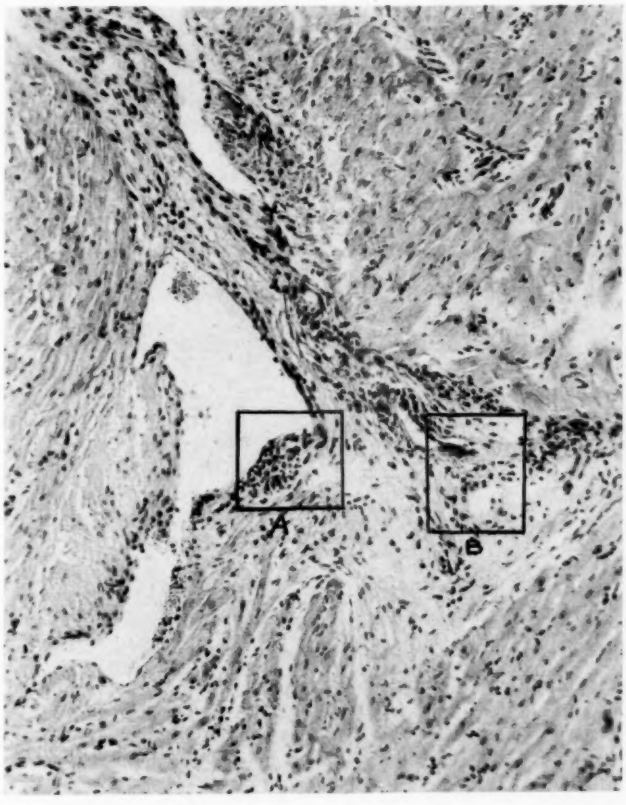

Fig. 1.—Subendocardial lesion at *A*, consisting of a localized collection of cells. At *B*, a multinucleated giant cell is seen. Hematoxylin and eosin stain; magnification ×100, reduced ¼. See Figs. 2 and 3 for cellular detail.

RESULTS

The majority of the guinea pigs infected with *Br. suis* showed only minimal clinical evidence of infection. Some developed transient arthritis of either the tarsal or carpal joints and failed to gain weight as rapidly as did the control group of normal guinea pigs. A few experienced an acute illness accompanied by loss of weight and ruffled fur. In several instances, ophthalmia and neurologic signs of disease developed. Three guinea pigs, Nos. 11, 25, and 37, died with brucellosis, 58, 65, and 242 days, respectively, after inoculation. With the exception of these three, all of the guinea pigs inoculated with *Br. suis* showed

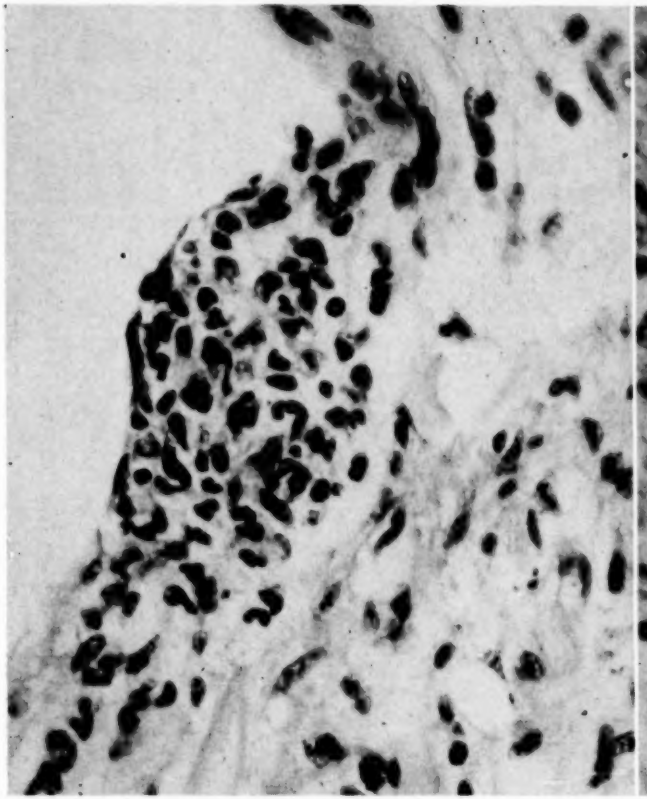

Fig. 2.

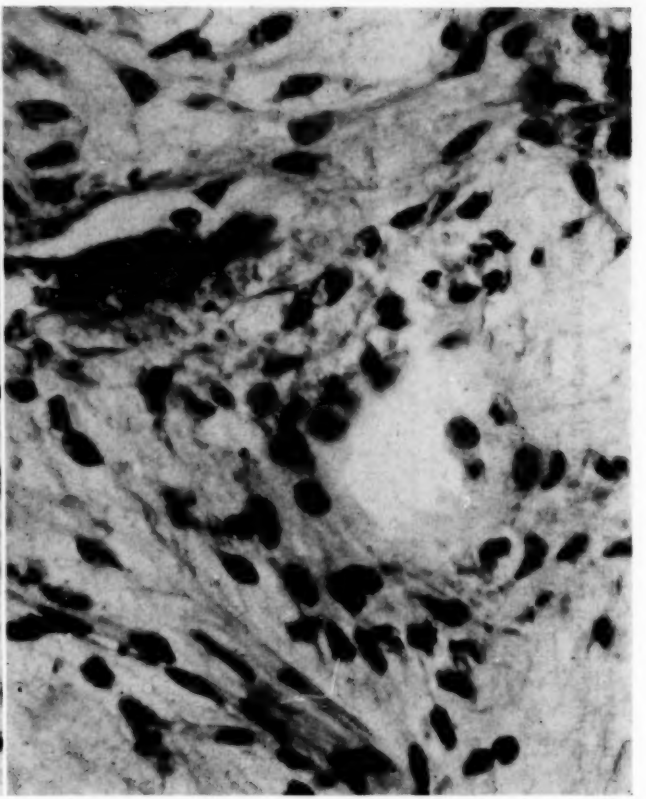

Fig. 3.

Fig. 2.—Subendocardial lesion in Fig. 1. Beneath the endothelium are collections of cells, most of which appear to be fixed tissue or mesenchymal cells. An occasional lymphoid cell is seen and Anitschkow "myocytes" with caterpillar nuclei and owl-eyed nuclei in the peripheral portion of the lesion. A resemblance to the lesion of acute rheumatic endocarditis may be observed. Hematoxylin and eosin stain; magnification ×700, reduced ¼.

Fig. 3.—From Fig. 1,*A*, showing multinucleated giant cell, numerous Anitschkow cells, and cells resembling fibroblasts. Hematoxylin and eosin stain; magnification ×700, reduced ¼.

Fig. 4.

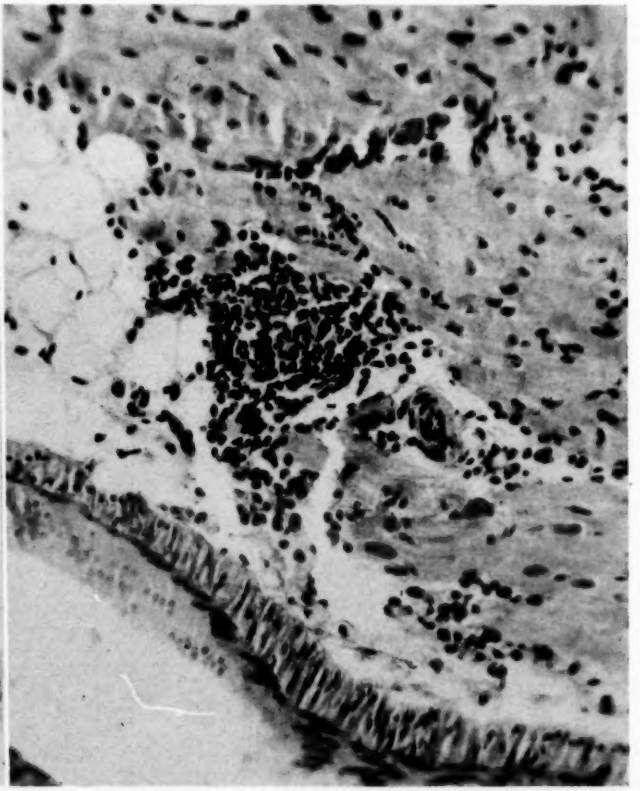

Fig. 5.

Fig. 4.—Subendocardial lesion showing fibrinoid necrosis with cellular reaction consisting of fibrocytes, macrophages, occasional lymphocyte, and a few polymorphonuclear leukocytes. A resemblance to the lesion of acute rheumatic endocarditis may be observed. Hematoxylin and eosin stain; magnification ×300, reduced ¼.

Fig. 5.—Epicardial, perivascular granulomatous lesion consisting chiefly of fixed tissue cells and lymphoid cells. Hematoxylin and eosin stain; magnification ×300, reduced ¼.

evidence of infection at the time of autopsy, as indicated by either the isolation of the organism from the blood of the spleen or heart or by the demonstration of specific agglutinins.

The guinea pigs infected with *Br. abortus*-strain 19 showed little clinical evidence of disease. Of the 10 pigs inoculated with *Br. abortus*, 3 failed to show either agglutinins or organisms in culture. The uninfected guinea pigs maintained as controls remained well.

Gross Pathologic Findings.—Macroscopically, the guinea pigs infected with *Br. suis* showed typical granulomatous lesions of experimental brucellosis in the spleen, lymph nodes, liver, joints, and epididymides, as described in the literature by Fabyan[14] and by Braude.[15] The gross appearance of the heart, how-

TABLE I. BACTERIOLOGIC AND SEROLOGIC OBSERVATIONS ON GUINEA PIGS EXPERIMENTALLY INFECTED WITH BRUCELLA SUIS AND SUBSEQUENTLY EXAMINED FOR CARDIOVASCULAR DISEASE

NUMBER	DAYS BETWEEN INOCULATION AND AUTOPSY	BRUCELLA AGGLUTININ TITER	SPLEEN CULTURE FOR BRUCELLA
8.	116	1–10240	Negative
9.	257	1– 2560	Positive
11.	242	——	——
13.	249	1– 2560	Negative
15.	257	1– 2560	Negative
16.	163	1– 2560	——
17.	246	1– 2560	Positive
25.	58	——	——
26.	383	1– 5120	Positive
27.	125	1– 5120	Positive
32.	205	1–10240	Positive
34.	153	1– 2560	Positive
35.	102	1– 5120	Positive
36.	97	1– 2560	Negative
37.	65	——	——
40.	136	——	Positive
42.	76	1– 1280	Positive
43.	82	1– 5120	——
44.	96	1– 2560	Positive
45.	136	1– 2560	——
46.	136	1–10240	Positive
49.	107	1–10240	Positive
54.	120	1– 5120	Positive
58.	178	1– 2560	——
62.	77	1– 1280	Positive
63.	98	1– 2560	Positive
67.	100	——	——
76.	46	1– 5120	Negative
85.	64	1– 5120	Negative
87.	253	1– 160	Positive
88.	250	1– 2560	Negative
98.	98	1– 1280	Positive
123.*	64	1– 80	Negative
141.*	70	1– 40	Negative
142.*	39	1– 160	Negative
143.*	70	1– 80	Negative
158.†	6	1– 640	Negative

*Inoculated with *Brucella abortus*.
†Mother infected with *Brucella suis*. Examined 6 days after birth.

ever, was normal. To our knowledge, gross involvement of the heart has not been described in experimental brucellosis. The guinea pigs inoculated with *Br. abortus*–strain 19 showed few or no lesions, and the group of normal controls was free from gross evidence of disease.

Microscopic Pathologic Findings.—Of the 32 guinea pigs infected with *Br. suis* whose hearts were examined, 15, or 46.8 per cent, showed microscopic lesions which were considered to be the result of the experimental infection. Four other animals infected with *Br. suis* had questionable small increases in Anitschkow myocytes. No lesions were observed in the hearts of the remaining 17. The hearts of the normal guinea pigs and those inoculated with *Br. abortus*–strain 19 likewise revealed no pathologic changes.

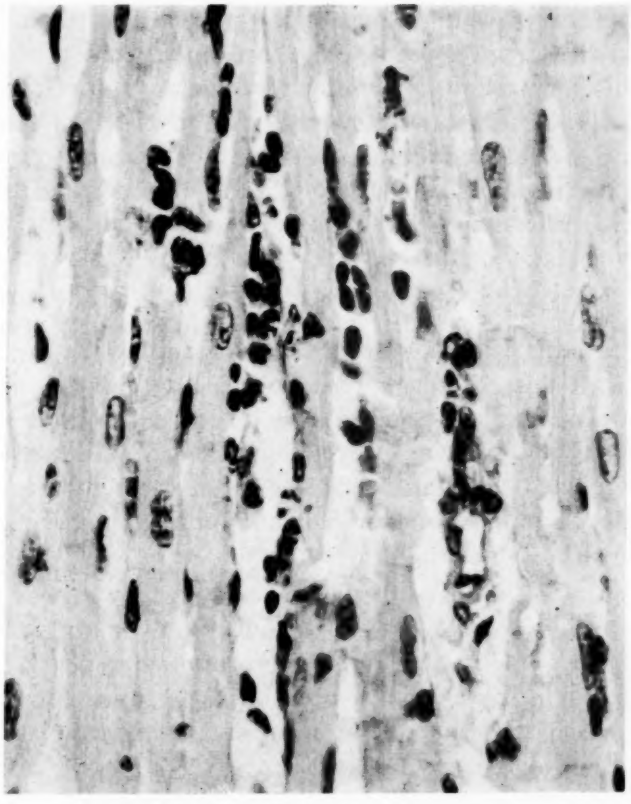

Fig. 6.—Focal areas of interstitial myocarditis with fixed tissue cell proliferation and occasional lymphoid cell. Hematoxylin and eosin stain; magnification ×700, reduced ¼.

The lesions were predominantly located either in the endocardium or in the epicardium, with a smaller number in the myocardium. Generally, the lesions were localized perivascularly. Only one guinea pig, No. 8, showed evidence of a necrotizing lesion of a vessel wall.

The lesions, in general, may be classified into three groups. *Group 1* included inflammatory lesions in the epicardium which consisted of collections of lymphocytes, plasma cells, and rare polymorphonuclear leukocytes in an edematous

connective tissue stroma. Eosinophils were not seen (Figs. 1,*B* and 3). *Group 2* (Figs. 1,*A*, 2, 4, 5) included granulomatous lesions, frequently subendocardial but also located in the epicardium and, occasionally, in the myocardium. These granulomatous lesions generally consisted of fixed tissue or mesenchymal cells which varied in size and shape and could probably be classified as macrophages. Small areas of necrosis were occasionally seen in the center of such lesions, but typical fibrinoid necrosis was not seen. Some of the lesions also contained inflammatory cells, mainly lymphocytes and polymorphonuclear leukocytes. Such lesions resemble some of the changes seen in acute rheumatic endocarditis. *Group 3* (Fig. 3) included areas of apparent interstitial myocarditis, with proliferation of fixed tissue cells and occasional lymphoid cells.

In all sections the increase in Anitschkow cells was far more prominent than in normal controls. While occasionally such areas resembled an Aschoff body, an unequivocal Aschoff type of granuloma was not observed (Fig. 3). The hearts in this series showed no valvular involvement. (However, in one of the animals, No. 24, in a later series, a granulomatous lesion was present at the base of the mitral valve.) It is significant that the lesions are not numerous in any one section and are not so diffusely distributed as in rheumatic fever. In general, one or two lesions are seen in a section.

DISCUSSION

The production of lesions by an experimental infection in animals must be interpreted with considerable care inasmuch as intercurrent infection may develop during an observation period. When inoculated animals develop specific evidence of disease, however, as proved by serologic and bacteriologic examination, and when the lesions produced are far more numerous and vary from a nonspecific lesion, one may be justified in assuming that such lesions resulted from the experimental inoculation.

In experimental brucellosis, cardiac lesions were produced in a significant number of guinea pigs inoculated with *Brucella suis* but not in those inoculated with *Brucella abortus*–strain 19. In the literature, reference is rarely made to cardiac involvement in experimental brucellosis in guinea pigs. Only Fabyan[14] made reference to examination of the heart and, in photomicrographs, showed a perivascular lesion in the epicardium. Braude,[15] on the other hand, in an extensive study of experimental brucellosis, made no reference whatever to examination of the hearts. Most investigators have examined microscopically only those tissues which show macroscopic lesions, and because the heart, in experimental brucellosis, reveals no gross abnormalities, the cardiovascular pathology has received little attention.

Whether cardiac lesions similar to those of rheumatic fever can be produced in experimental brucellosis depends upon interpretation of the lesions. In our opinion, proliferation of Anitschkow myocytes does not necessarily constitute formation of an Aschoff body. Large or multinuclear cells such as those seen in Aschoff bodies were not observed in the experimental cardiac lesions. Furthermore, fibrinoid degeneration was not noted. On the other hand, many of the

lesions were not unlike the nonspecific endocardial, epicardial, and myocardial lesions consisting of cells resembling macrophages with some circulating inflammatory cells. Rich[16] described five cardiac lesions characteristic of rheumatic fever: (1) focal alterations in the collagen of the connective tissue, (2) the presence of the Aschoff body, (3) focal and diffuse inflammatory lesions, (4) focal alterations in cardiac muscle, and (5) verrucous valvular lesions. In our series thus far, three of the above criteria, namely, focal alterations in the collagen, focal inflammatory lesions, and focal alterations in the cardiac muscle, were observed. Furthermore, in a recent animal a granulomatous lesion at the base of the mitral valve was observed. The more specific lesions of rheumatic fever, namely, Aschoff bodies and verrucous valvular lesions, were not definitely established after a single inoculation of Brucella. Certain lesions may be referred to as Aschoff-like bodies, however. The fact that typical Aschoff bodies were not observed may be due to the experimental host's reaction to the infection, which might be at variance with the reaction in man. Studies employing multiple injections to determine the type of lesions which may develop are in progress. Thus, these findings suggest that in human beings, brucellosis may cause certain lesions not unlike those present in rheumatic fever. In a recent report, Saphir[17] reviewed the morphologic findings in what he considers a true Aschoff body and stated, "Strictest criteria of what constitutes an Aschoff body are of utmost importance, not only from the morphologic point of view to recognize true rheumatic heart disease but especially for experimental and etiologic reasons. . . . As stated, it is wiser to err and call a lesion 'doubtful' and not make a definite and specific diagnosis than to designate lesions somewhat resembling Aschoff bodies as true Aschoff bodies."

SUMMARY

Cardiac pathology in 37 guinea pigs was studied at intervals of from 39 to 383 days after a single inoculation with either *Brucella suis* or *Brucella abortus*–strain 19. Although definite microscopic cardiac lesions were present in 15, or 46.8 per cent, of the group infected with *Brucella suis*, they tended to resemble the so-called nonspecific lesions observed after injection with dead streptococci, foreign proteins, dysentery bacilli, serum, and a number of other substances. No lesions completely identical to Aschoff bodies were observed. The experimental evidence indicates that Brucella infection causes microscopic lesions in the heart of the guinea pig, and that the heart is not as resistant to the infection as was inferred from gross examination.

The authors are grateful to Kathryn M. Miller for technical assistance and to Ruth H. Konwaler for preparation of the microscopic sections. Dr. W. C. Manion of the Armed Forces Institute of Pathology kindly reviewed the sections from several of the cases herein reported.

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The Influence of High Altitudes on the Electrical Activity of the Heart. I. Electrocardiographic and Vectorcardiographic Observations in the Newborn, Infants, and Children

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A moderate arterial oxygen unsaturation, hypervolemia, and polycythemia are common findings in healthy residents of high altitudes.[1-3] In these subjects, anatomic and electrocardiographic evidence of right ventricular hypertrophy and a mild pulmonary hypertension have been also demonstrated.[4-8] These observations were made in adults. However, it was unknown whether such findings were present since birth or were acquired later as a consequence of the acclimatization to an environment of chronic anoxic anoxia. Therefore, we thought it would be interesting to make electrocardiographic and vectorcardiographic studies in the native newborn, infants, and children of the high altitudes.

MATERIAL AND METHODS

The criteria for the differentiation between "normal" and "abnormal" in electrocardiography have not been well defined statistically.[9-11] There is a characteristic evolutionary pattern of the normal electrical activity of the heart from birth to old age. Therefore, age is the most important variable in evaluating the normality of the electrocardiogram. However, with the exception of Ziegler's work, an inadequate distribution of age groups is observed in most of the studies in normal infancy and childhood. Furthermore, the statistical analysis of the data is frequently neglected, and the extreme values are commonly considered as normal limits.[13-19] For the same reasons, the criteria proposed for right ventricular hypertrophy in infancy and childhood are also doubtful.[20,21] Therefore, in order to study the influence of an environment of high altitude on the electrical activity of the heart, we thought it necessary to compare statistically the observations made in the newborn, infants, and children of high altitudes with those in subjects of similar age studied at sea level.

Three hundred and fifty normal children, ranging from newborn to 14 years of age, were studied in Lima, at sea level, and 190 were studied in Morococha, which is situated at 14,900 feet (4,540 meters) above sea level and has a mean barometric pressure of 446 mm. Hg. These children had always resided in their respective place of study. Table I shows the distribution

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of the cases in 5 age groups: newborn, 1 week to 3 months, 4 to 11 months, 1 to 5 years, and 6 to 14 years. The newborn infants were studied within 10 minutes after birth. In 10 subjects at sea level and in 10 at high altitude the electrocardiographic evolution was studied from birth up to 3 months of age. In none of the subjects was a hypnotic medication used.

A Sanborn Viso-Cardiette, Model 52, electrocardiograph was used. Conventional leads and additional chest leads were taken in each case. The vectorcardiograms were recorded according to Grishman's reference system,[22] using a Sanborn Vector Amplifier, Model 185, coupled to a Sanborn Viso-Scope, Model 169A, and a Polaroid Fairchild camera, Model F-296A.

Fisher's t-test was used in order to estimate the statistical significance of the differences between the mean values obtained at sea level and those at high altitudes.

TABLE I. DISTRIBUTION OF CASES ACCORDING TO AGE

	NEWBORN	1 WK.-3 MO.	4-11 MO.	1-5 YR.	6-14 YR.	TOTAL
Lima (At sea level) B.P.:749	50	50	50	100	100	350
Morococha (14,900 ft.) B.P.:446	15	50	25	50	50	190

B. P.: Mean barometric pressure (mm. Hg).

RESULTS

The auricular activation process and the auriculoventricular conduction time were normal in healthy children of high altitudes. The most important findings were observed in the ventricular activation and repolarization processes.

Ventricular Activation Process.—

1. *The mean QRS vector:* In the newborn, the frontal projection of the mean spatial QRS vector (ÂQRS) showed an accentuated right deviation both in Lima and in Morococha (Figs. 1-3). With age, ÂQRS shifts rapidly to the left at sea level, whereas at high altitude the marked right ÂQRS deviation persists through-

TABLE II. THE ÂQRS° POSITION

		NEWBORN	1 WK.-3 MO.	4-11 MO.	1-5 YR.	6-14 YR.
Sea Level	Mean ± S.E.	145 ± 2.8	110 ± 3.9	69 ± 3.1	57 ± 3.0	57 ± 2.8
	S.D.	20.1	27.2	21.5	28.0	27.7
	Extreme Values	80 −175	60 180	0 100	−30 110	−40 105
Morococha (14,900 ft.)	Mean ± S.E.	133 ± 7.9	152 ± 4.5	155 ± 7.6	155 ± 6.4	137 ± 6.6
	S.D.	28.5	32.1	38.1	44.9	46.2
	Extreme Values	100 −165	100 −150	90 −125	80 −95	65 −110
t		1.74	6.96*	12.37*	15.72*	13.04*

*$p < 0.001$.
t: t values calculated by Fisher's t-test.
S.E.: Standard error. S.D.: Standard deviation.

out infancy and childhood (Figs. 1, 2, and 4). Table II shows the mean values obtained at sea level in comparison with those obtained at high altitudes. The difference is highly significant ($p < 0.001$) in all age groups, with the exception of the newborn. At high altitudes, the ÂQRS range increases progressively with age, and this agrees with the progressive increase in the standard deviation (Fig. 2 and Table II).

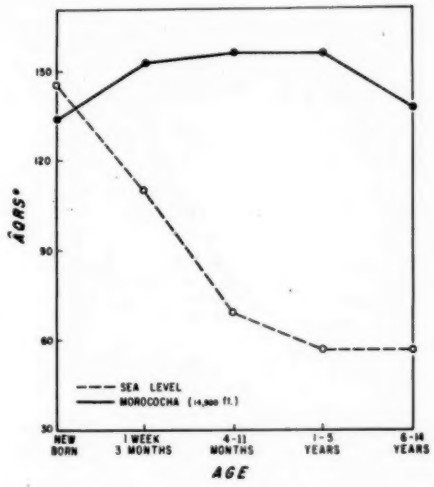


Fig. 1.—An accentuated right ÂQRS deviation in the newborn is a physiologic characteristic both at sea level and at high altitudes. With age, ÂQRS shifts rapidly to the left at sea level, whereas at high altitudes a marked right ÂQRS deviation persists throughout infancy and childhood.

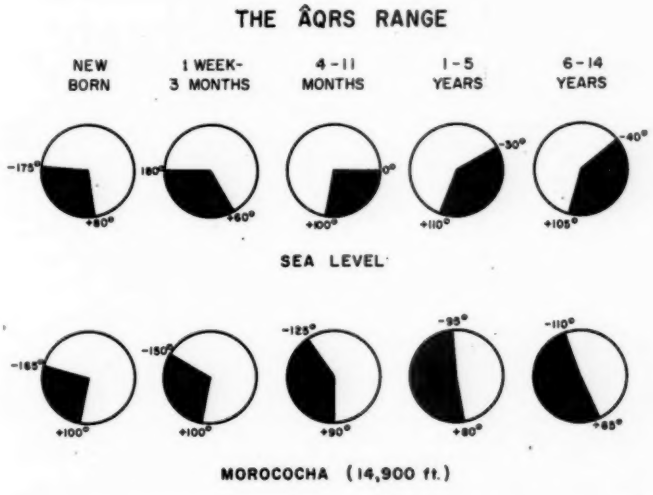


Fig. 2.—At sea level, the ÂQRS direction changes rapidly with age but the ÂQRS range shows only a little variation. At high altitudes an increase of the ÂQRS range with age is practically the only change observed.

2. *The QRS complex:* Complexes of rS or qrS type in Leads I, II, and aVL, qR or qRs patterns in Leads III and aVF, and qR or QR complexes in Lead aVR are common findings in the native infants and children of the high altitudes (Figs. 5,*B*, 6,*B*, 7,*B*, and 10). Complexes of rS and qrS type are also seen in Leads

II, III, and aVF when ÂQRS points upward (Fig. 8). At sea level, similar patterns are seen only in the newborn (Fig. 3,*A*) and in some infants of less than 3 months of age. Table III shows the voltage values of the late R wave, and the R′/Q or S ratio in Lead aVR. The predominance of the upward deflection in this lead is a common finding in high altitudes. With the exception of the newborn,

TABLE III. SCALAR DATA OF THE QRS COMPLEX IN LEAD aVR AND IN PRECORDIAL LEADS

			NEWBORN	1 WK.-3 MO.	4-11 MO.	1-5 YR.	6-14 YR.
R′ in aVR (in mm. = 0.1 mV.)	S. L.	Mean ± S.E. S. D. Extreme Values	4.8 ± 0.34 2.41 0 10	3.5 ± 0.29 2.06 0 12	3.8 ± 0.26 1.85 0 10	3.2 ± 0.18 1.78 0 9	1.8 ± 0.14 1.38 0 6
	H. A.	Mean ± S.E. S. D. Extreme Values	3.3 ± 0.56 2.01 0 7	5.1 ± 0.40 2.82 1 13	7.5 ± 0.68 3.38 2 18	6.2 ± 0.37 2.61 0 14	4.3 ± 0.28 2.01 1 9
		t	2.10	3.77*	6.14*	8.31*	9.18*
R′/Q or S in aVR	S. L.	Mean ± S.E. S. D. Extreme Values	2.5 ± 0.28 1.93 0 7.0	1.0 ± 0.17 1.23 0 6.0	0.4 ± 0.03 0.23 0 1.0	0.4 ± 0.03 0.28 0 1.7	0.2 ± 0.02 0.20 0 1.0
	H. A.	Mean ± S.E. S. D. Extreme Values	1.7 ± 0.49 1.62 0 5.0	3.1 ± 0.34 2.33 0.5 8.0	3.2 ± 0.57 2.84 0.5 11.0	1.8 ± 0.19 1.35 0 7.0	1.4 ± 0.16 1.12 0.1 6.0
		t	0.93	5.61*	6.93*	10.49*	10.16*
R in V_1 (in mm. = 0.1 mV.)	S. L.	Mean ± S.E. S. D. Extreme Values	18.3 ± 0.81 5.76 5 31	12.0 ± 0.78 5.51 3 34	12.8 ± 0.68 4.84 5 23	10.4 ± 0.45 4.45 3 23	6.2 ± 0.31 3.14 1 17
	H. A.	Mean ± S.E. S. D. Extreme Values	14.0 ± 1.56 5.61 6 22	17.1 ± 0.99 7.02 6 36	21.2 ± 1.49 7.43 10 35	14.6 ± 1.02 7.25 5 37	9.2 ± 0.65 4.59 1 22
		t	2.51	4.02*	5.92*	4.39*	4.78*
R/S in V_6	S. L.	Mean ± S.E. S. D. Extreme Values	0.7 ± 0.05 0.35 0.2 1.7	1.6 ± 0.11 0.77 0.2 3.6	2.6 ± 0.28 2.0 0.6 9.6	2.9 ± 0.17 1.72 0.7 11.1	4.9 ± 0.46 4.57 1.0 30.0
	H. A.	Mean ± S.E. S. D. Extreme Values	0.9 ± 0.19 0.64 0.3 1.5	0.8 ± 0.07 0.50 0.2 2.9	0.9 ± 0.16 0.81 0.2 2.1	1.7 ± 0.14 0.99 0.4 4.3	1.9 ± 0.18 1.25 0.5 7.5
		t	1.67	5.94*	3.82*	5.03*	4.50*
R in V_1 + S in V_5	S. L.	Mean ± S.E. S. D. Extreme Values	31.5 ± 1.10 7.80 16 47	22.6 ± 1.08 7.63 11 46	22.1 ± 0.88 6.24 11 38	18.4 ± 0.61 6.11 8 37	11.2 ± 0.40 4.05 4 24
	H. A.	Mean ± S.E. S. D. Extreme Values	25.8 ± 1.54 5.36 19 35	32.2 ± 1.38 9.77 9 58	36.4 ± 2.04 10.18 21 53	24.6 ± 1.30 9.24 11 46	17.7 ± 0.84 5.97 7 34
		t	2.42	5.47*	7.58*	4.94*	7.81*

*$p < 0.001$

t: t values calculated by Fisher's t-test.

S.L.: Sea level. H.A.: High altitudes (Morococha—14,900 ft.).

the difference between the mean values obtained at sea level and those at high altitudes is highly significant. The "transitional pattern" of the standard limb leads, characterized by RS or qRS complexes in Lead I and QR or rSR′ in Lead III, was never observed in high altitudes. This pattern is frequently seen at sea level in children between 3 months and 3 years of age, coinciding with a "transitional pattern" of the QRS loop in the frontal projection (Fig. 5,*A*).

Complexes of Rs type in infants, and RS or rS patterns in children are found in Lead V_1 in the high altitudes. However, there is no close correlation with age as occurs at sea level; it is not rare to find Rs patterns in older children and RS complexes in some infants (Figs. 4, 5,*B*, 6,*B*, 7,*B*, 8, and 10). The voltage of the R wave in Lead V_1 is higher in high altitudes than at sea level, and the difference between the mean values is highly significant in infancy and childhood (Table III).

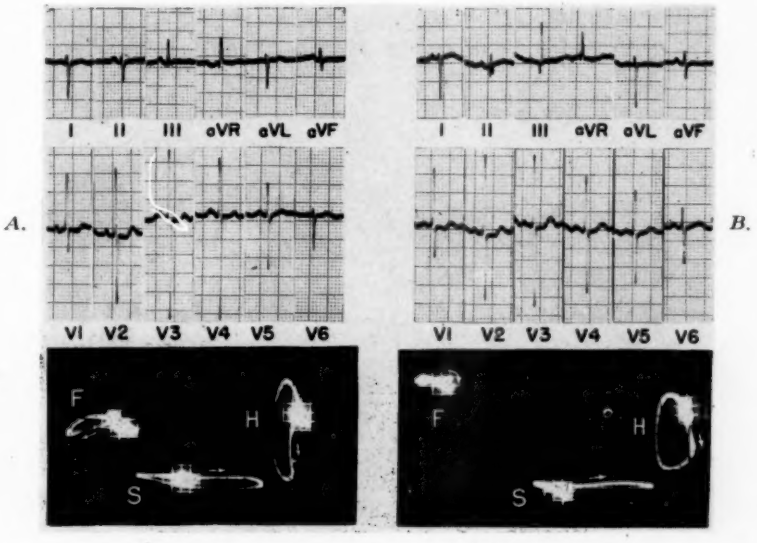


Fig. 3.—In the newborn, the electrocardiographic and vectorcardiographic characteristics are similar both at sea level (*A*) and at high altitudes (*B*). An accentuated right ÂQRS deviation is seen, and the QRS loop is oriented to the right and anteriorly, showing clockwise rotation in the frontal and transverse projections. The T loop is oriented to the left and anteriorly, and positive T waves are found in the right precordial leads.

The values corresponding to the QRS duration and the time of appearance of the "intrinsicoid deflection" did not show significant difference from the figures obtained at sea level. The R′ pattern in Lead V_1 with a normal QRS duration was not seen in the high altitudes, whereas it is frequently found at sea level in children between 3 months and 3 years of age, coinciding with a "transitional pattern" of the QRS loop in the transverse projection (Fig. 5,*A*). The qR complexes are common in the right additional chest leads, and rsR′ patterns or M-shaped QRS complexes are frequently seen in the upper additional chest leads, particularly in the region of the angle of Louis (Fig. 10).

Complexes of rS, RS, Rs, qRS, or qrS type are seen in the left precordial leads. A deep S wave is a common finding, whereas the Q wave is rarely observed

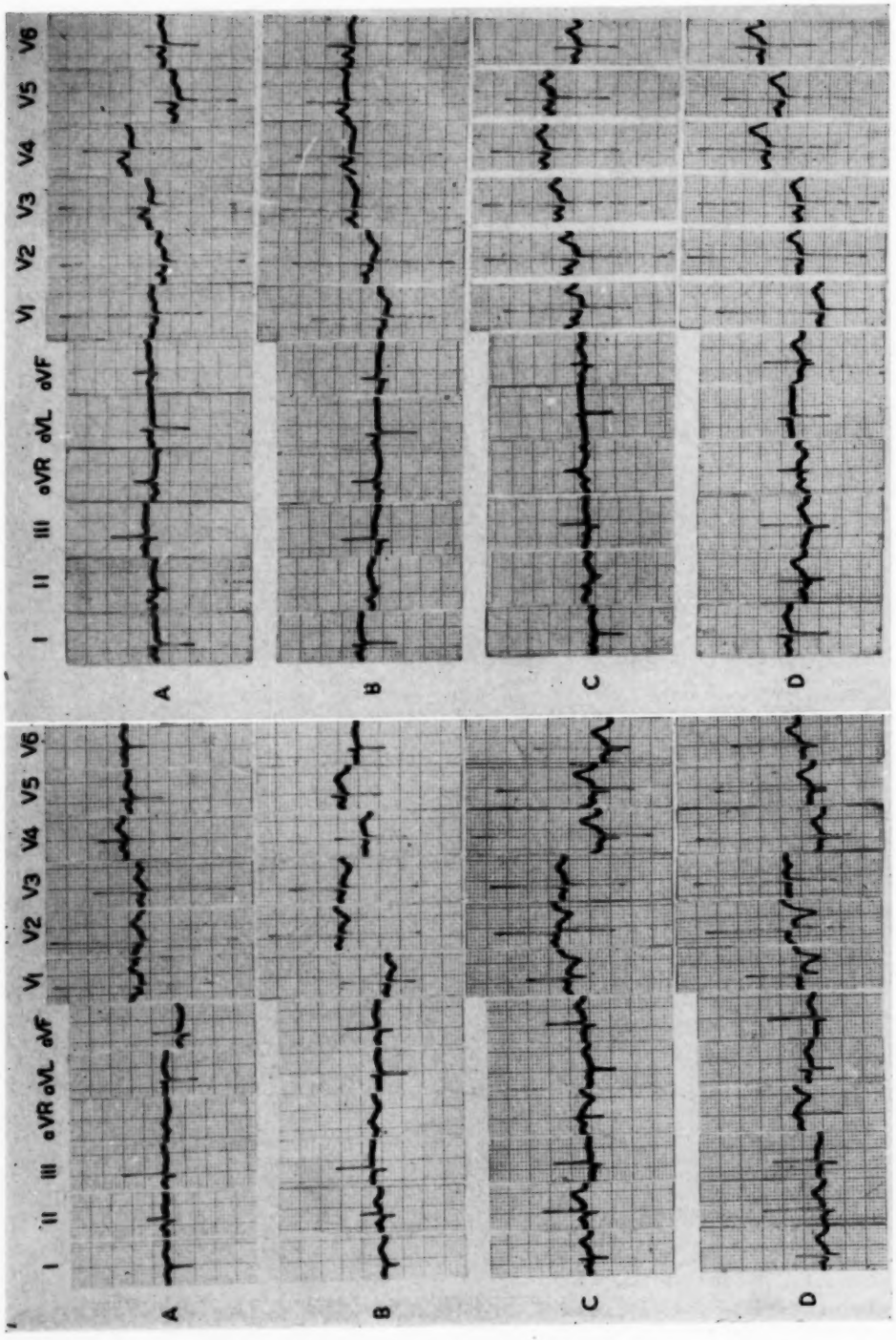
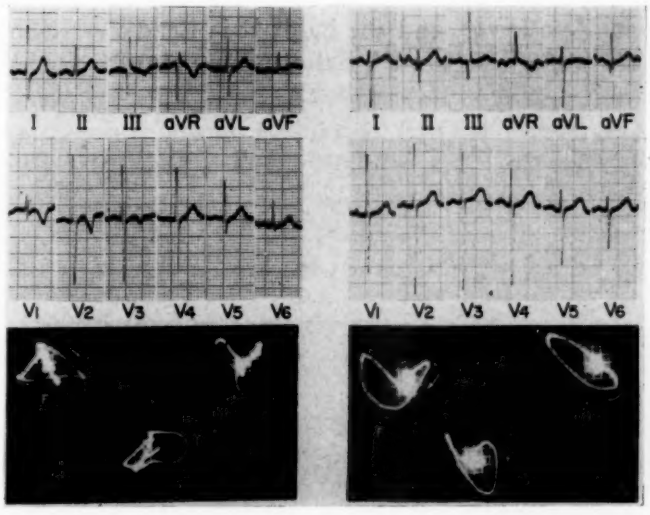
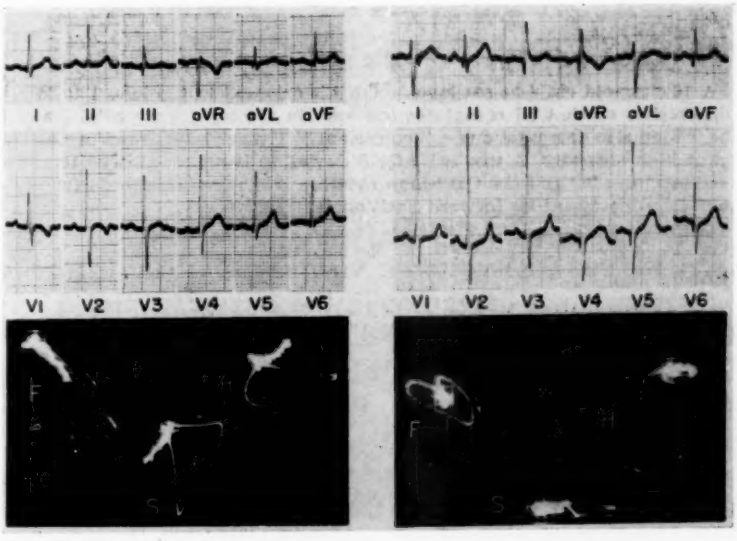


Fig. 4.—Evolutionary pattern of the ECG changes during the first three months of life at sea level (*left*) and at high altitudes (*right*). *A*, Newborn infant. *B*, One week after birth. *C*, At 1 month of age. *D*, At 3 months of age. ÂQRS shifts rapidly to the left at sea level, whereas a marked ÂQRS deviation is maintained at high altitudes. The "infantile" T-wave pattern is promptly attained at sea level, but at high altitudes the T wave becomes positive again in the right precordial leads after the first week of life.



A. *B.*

Fig. 5.—*A*, A normal 3-month-old infant at sea level, showing "transitional" QRS patterns in the standard limb leads (RS in I and QR in III) and in Lead V_1 (rsr's' complex), and "transitional" QRS loops in the frontal and transverse views. The "infantile" T-wave pattern is present in the right precordial leads. *B*, A normal 3-month-old infant at high altitudes. The "transitional" QRS patterns are absent. ÂQRS points toward ±180°, and the terminal QRS vectors show an increased magnitude which explains the deep S waves in all precordial leads.

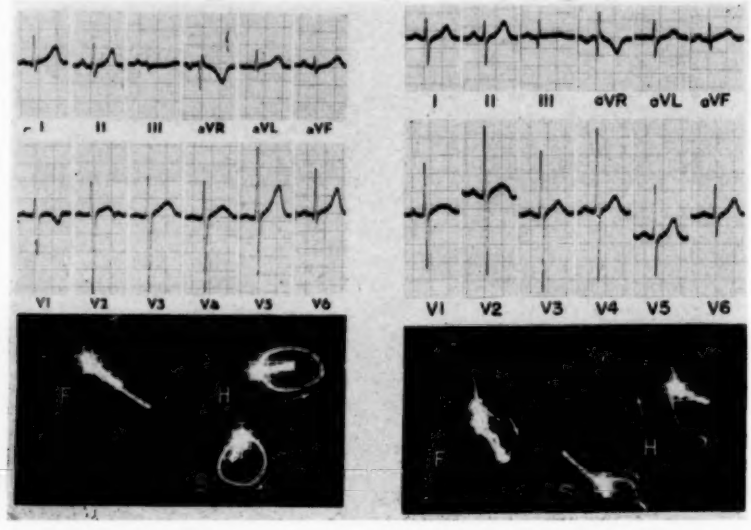


A. *B.*

Fig. 6.—*A*, A normal 2-year-old infant at sea level. ÂQRS points to the left. The QRS loop is narrow in the frontal view and it rotates counterclockwise in the transverse projection. The T loop shows a backward position, and the T wave is downward in the right precordial leads. *B*, A normal 2-year-old infant at high altitudes. ÂQRS is placed at +135°. The QRS loop is wide in the frontal projection, and a clockwise QRS rotation is seen in the horizontal view. The T loop is oriented anteriorly, so that positive T waves are present in the right precordial leads.

(Figs. 4, 5,*B*, 6,*B*, 7,*B*, and 8). In comparison with studies made at sea level, the R/S ratio in Lead V_5 is lower, and the index R in Lead $V_1 + S$ in Lead V_5 shows higher values. The difference between the mean values is highly significant in infancy and childhood (Table III).

3. *The QRSsÊ loop:* The QRS loop in the newborn presents the same characteristics both at sea level and at high altitudes. It is directed forward, to the right and slightly downward, showing a clockwise rotation in the frontal and horizontal projections (Fig. 3, *A* and *B*). Later on, with age, the evolutionary changes of the QRS loop are different at sea level and at high altitudes (Fig. 11).



A. *B.*

Fig. 7.—*A*, A 10-year-old child at sea level. ÂQRS is oriented to the left. The forward direction of the QRS loop diminishes so that rS complexes are seen in the right precordial leads. The backward orientation of the T loop also decreases and a "transitional" T wave is observed in Lead V_2. *B*, A normal 10-year-old child at high altitudes. A marked ÂQRS deviation is observed. The terminal QRS vectors show an increased magnitude, and the QRS-loop rotation is clockwise in both frontal and horizontal projections. The T loop maintains its forward position.

At sea level, the mid-QRS vectors deviate rapidly to the left, and a "figure-of-eight" QRS rotation is not infrequent in the transverse projection (Fig. 5,*A*). After 3 months of age, the QRS loop is directed to the left and anteriorly, and a "figure-of-eight" or counterclockwise QRS rotation is common in the horizontal view (Fig. 6,*A*). After 3 years of age, the forward direction of the QRS loop diminishes slowly, and some years later the mid-portion of the QRS loop, including the maximal QRS vector, is oriented posteriorly, to the left and inferiorly. The small early QRS vectors are directed to the right and anteriorly, and the late QRS vectors point to the right and posteriorly. The QRS loop rotates clockwise in the right sagittal projection, counterclockwise in the horizontal plane, and it is narrow in the frontal view, showing clockwise, counterclockwise, or "figure-of-eight" QRS rotation in this projection (Fig. 7,*A*).

A marked delay in the evolutionary pattern of the QRS loop with age occurs in the high altitudes. At 3 months of age, the characteristics seen in the newborn

persist (Fig. 9, *A*, *B*, *C*), and in some cases one may observe an increased magnitude of the terminal QRS vectors (Fig. 5,*B*). After 3 months of age, the QRS loop changes slowly, so that similar vector loops can be found in native infants and children of the high altitudes. The orientation of the initial QRS vectors

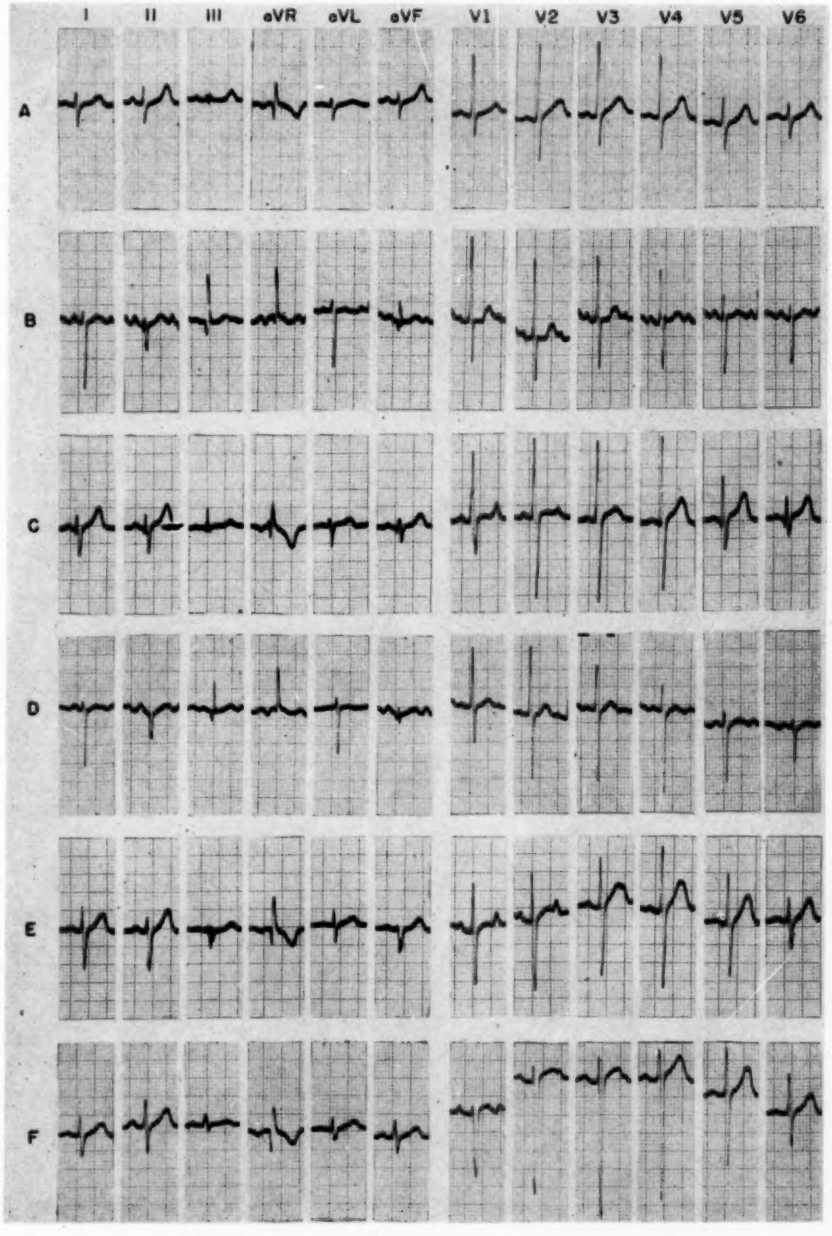


Fig. 8.—Electrocardiographic patterns in children of high altitudes. *A*, *B*, *C*, Children less than 3 years of age. *D*, *E*, *F*, Children more than 3 years of age. ÂQRS shows a marked right deviation, usually more than +150°. Complexes of rS, qrS or RS type are frequently found in Leads I and II. Complexes of Rs type in infants, and RS or rS patterns in children are found in Lead V_1. However, Rs patterns can be seen in older children, and RS complexes in some infants. Positive T waves are commonly observed in the right precordial leads.

persist to the left, upward and forward, the mid-vectors are directed anteriorly and slightly to the left, and the terminal QRS vectors, of increased magnitude, are directed to the right, superiorly and posteriorly. The QRS loop is wide in the frontal view and it rotates clockwise in this projection. Clockwise or counterclockwise QRS rotation is seen in the right sagittal view, and clockwise or rarely a "figure-of-eight" rotation is seen in the transverse projection (Fig. 9, *D*, *E*, *F*).

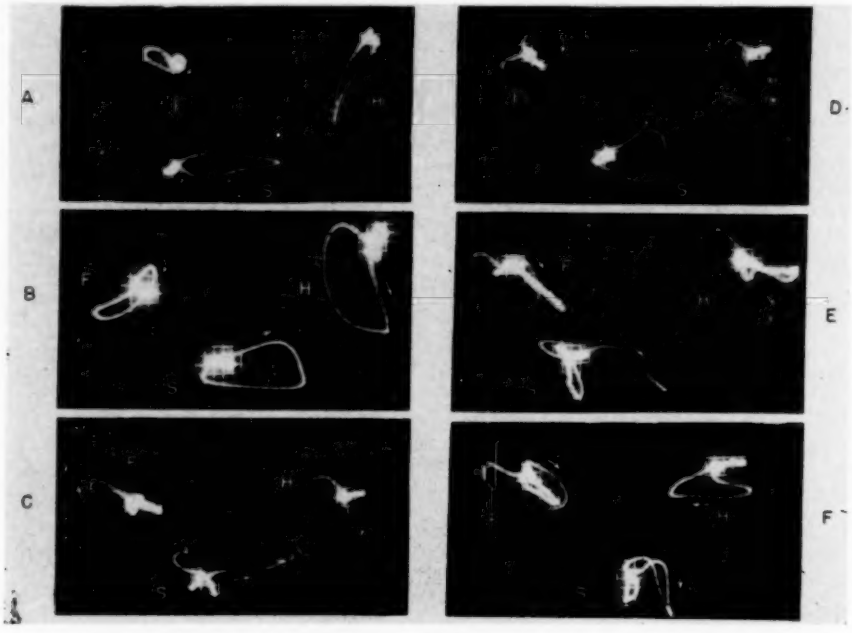


Fig. 9.—Vectorcardiographic patterns in children of high altitudes. *A*, *B*, *C*, Children less than 3 months of age. *D*, *E*, *F*, Children more than 3 months of age. The VCG pattern observed in the newborn is practically unchanged up to 3 months of age. Later on, the mid-QRS vectors are directed slightly to the left, and the late vectors frequently show an increased magnitude. The QRS loop is wide in the frontal view, and it shows a clockwise rotation in both frontal and transverse projections.

Ventricular Repolarization Process.—The ventricular recovery process in the newborn has similar characteristics at sea level and at high altitudes. The T loop is directed to the left, inferiorly and anteriorly, and the T wave is positive in the right precordial leads. However, an incipient inversion in the early portion of the T wave and latter part of the RS-T segment is a frequent finding in these leads (Figs. 3, *A* and *B*). A little later, in a period that varies between a few hours and 3 days after birth, the T loop shifts to a backward position and the T wave becomes negative in the right precordial leads, but the "infantile" T-wave pattern is not yet clear (Fig. 4). This change was observed in both Lima and Morococha, and only a few weeks later did the difference between the two places become evident (Figs. 4 and 11).

At sea level, the backward T-loop position is maintained and the "infantile" T-wave pattern is now evident, being negative, deep and asymmetrical in the right precordial leads (Figs. 4, 5,*A*, and 6,*A*). Later on, these characteristics diminish

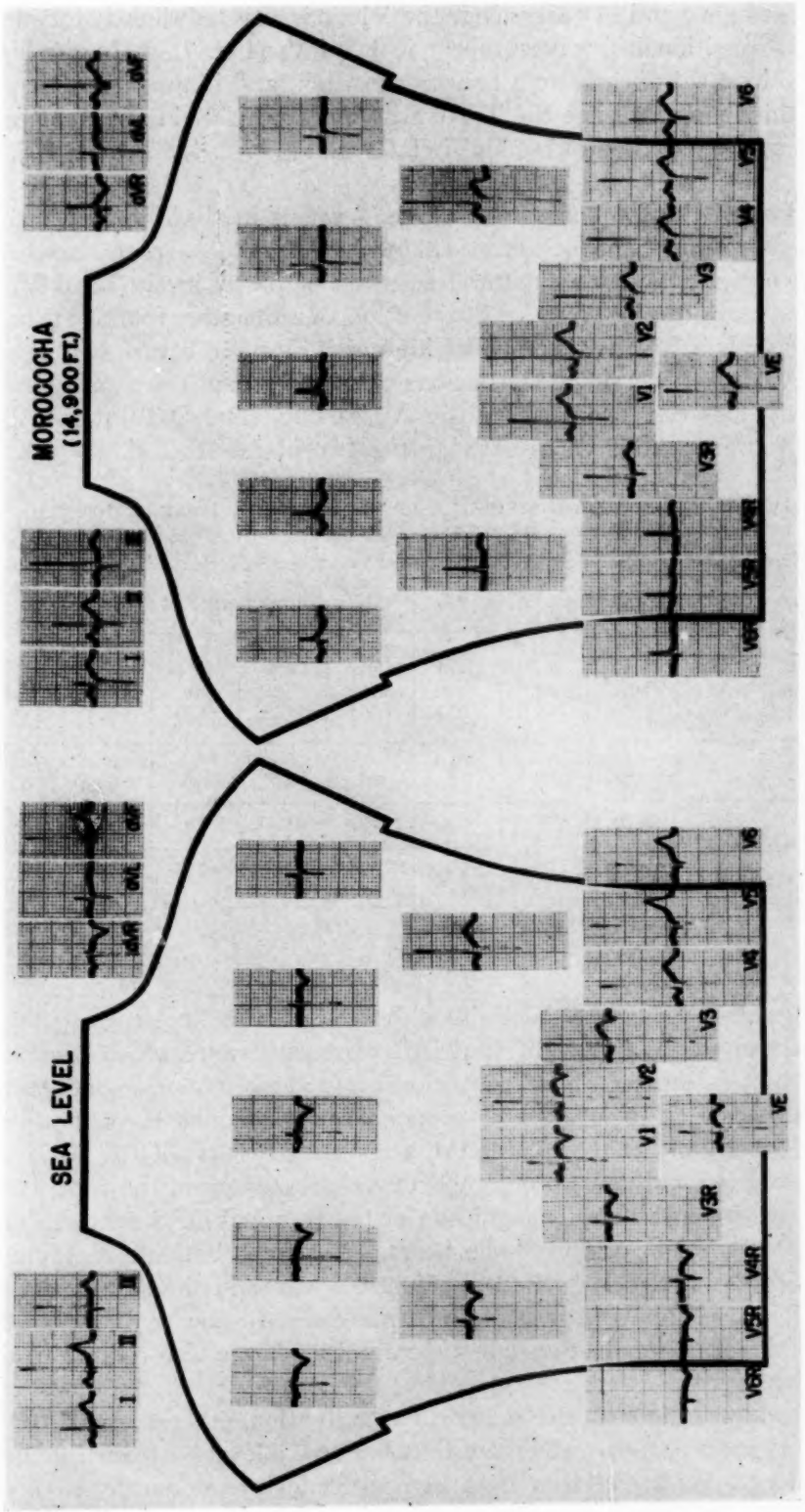


Fig. 10.—Two normal 7-year-old children, one at sea level and the other at high altitudes. In the right lower additional chest leads, rS or rSr′ patterns are found at sea level, whereas Rs or qR complexes are seen at high altitudes. In the right upper additional chest leads, an rSr′ pattern is observed at sea level, whereas qR, rsR′, or M-shaped QRS complexes are found at high altitudes.

slowly, and at between 6 and 14 years of age the T loop is directed slightly forward, and positive or transitional T waves appear in Lead V_2 (Fig. 7,*A*). In the high altitudes, the T loop shifts early to a forward position, and between the second week and the third month of age the T wave becomes positive in the right precordial leads, a characteristic that remains in later years (Figs. 4, 5,*B*, 6,*B*, 7,*B*, 8, and 10).

A comparison of the frequency of positive T waves in the right precordial leads at sea level and at high altitudes is shown in Table IV. In the newborn the T wave is upright, and the greater frequency of positivity in Lead V_1 is explained by the very anterior direction of the T loop. In the other four age groups a positive T wave is a frequent finding at high altitudes and a rare one at sea level. At sea level, one observes the variations characteristic of the age.

The mean values corresponding to the ÂT position and Q-T interval did not show any significant differences between the two places studied.

TABLE IV. THE PERCENTUAL DISTRIBUTION OF THE UPRIGHT T WAVE IN THE RIGHT PRECORDIAL LEADS

	SEA LEVEL					MOROCOCHA (14,900 FT.)				
	NEW BORN (%)	1 WK. 3 MO. (%)	4-11 MO. (%)	1-5 YR. (%)	6-14 YR. (%)	NEW BORN (%)	1 WK. 3 MO. (%)	4-11 MO. (%)	1-5 YR. (%)	6-14 YR. (%)
V_1	88	0	0	0	18	93	24	60	60	64
V_2	86	4	0	19	69	90	50	80	76	68
V_3	78	22	64	66	95	77	70	92	86	86

DISCUSSION

Our findings at sea level agree basically with those of other investigators.[12,23-31] The newborn shows normally a right ventricular preponderance which decreases rapidly, and which is replaced by a physiologic left ventricular preponderance. At high altitudes the right ventricular preponderance remains throughout infancy and childhood, and that explains the accentuated right ÂQRS deviation and the tall R wave in Lead V_1. Another important characteristic of the ventricular activation process is an increased magnitude of the terminal QRS vectors. This finding, and not a special position of the heart, determines both the tall late R wave in Lead aVR and the deep or predominant S waves in the standard limb leads, in the left precordial leads, and, in some cases, in the right precordial leads. The positive T waves in the right precordial leads are also related to the right ventricular overload.[32,33]

The delayed evolution of the ventricular activation process explains the absence of transitional patterns which are frequent at sea level between 3 months and 3 years of age. When children from high altitudes are taken down to sea level, the ventricular activation process is accelerated, the vectors corresponding

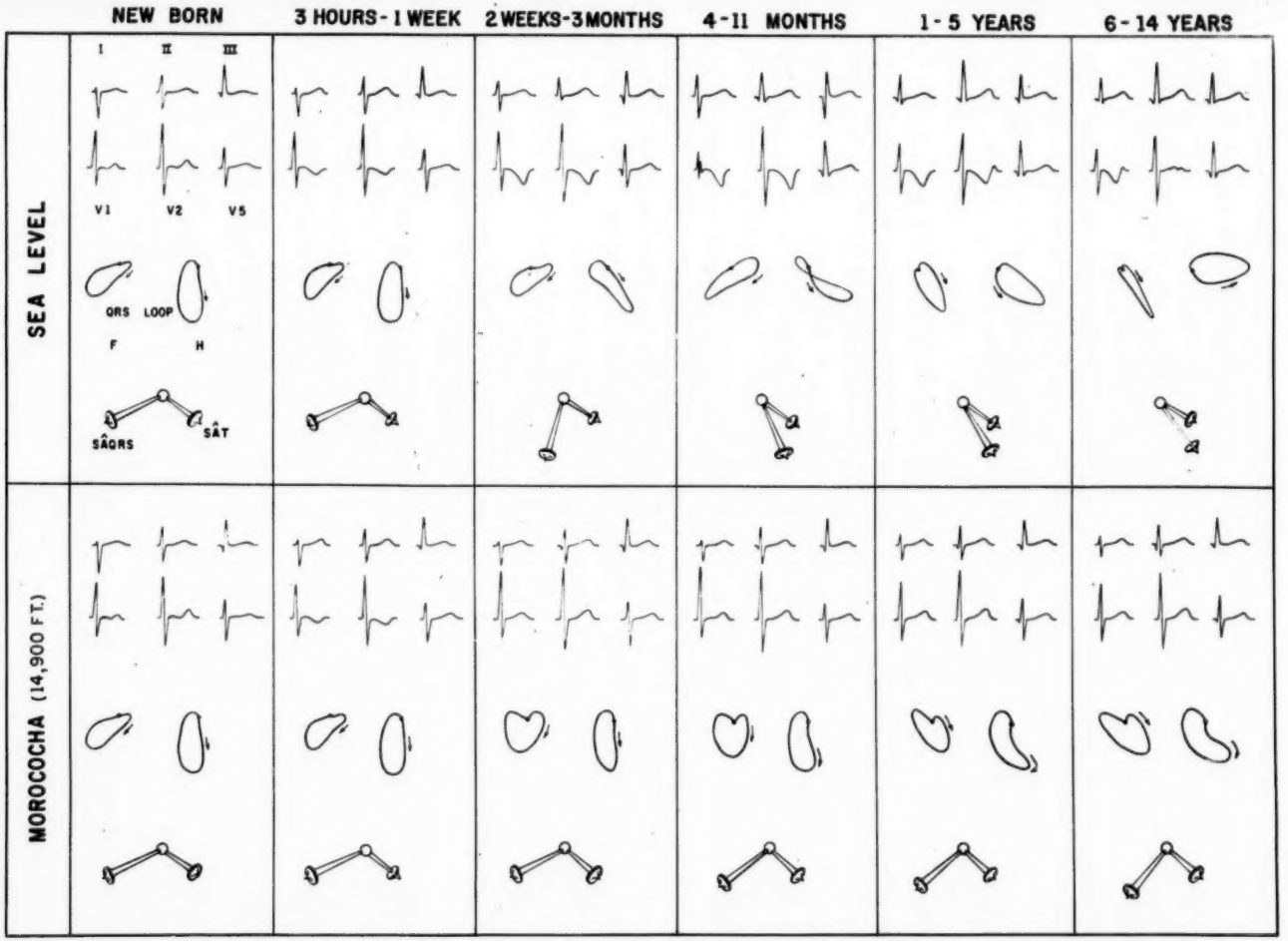


Fig. 11.—Schematic representation of the evolutionary pattern of the cardiac electrical activity from birth to 14 years of age. At sea level, ÂQRS changes rapidly, and "transitional" QRS patterns are frequently found between 3 months and 3 years of age. "Infantile" T-wave pattern is a common finding, except in the newborn. At high altitudes, a marked delay in the evolutionary pattern of the ventricular activation process is observed. The accentuated ÂQRS deviation persists throughout infancy and childhood, and positive T waves are frequently found in the right precordial leads.

to the left ventricular activation increase in magnitude, and transitional patterns can be observed.[34] These changes resemble in some way those observed postoperatively in certain congenital heart diseases associated with pulmonary stenosis.[35-37]

Differential Diagnosis With Pulmonary Stenosis.—A marked right ÂQRS deviation, a tall R wave in Lead V_1, and positive T waves in the right precordial leads are also common findings in cases of pulmonary stenosis with a right ventricular systolic pressure similar to that of the systemic circulation. This hemodynamic condition is seen in pulmonary stenosis with overriding aorta, and in some cases of pure pulmonary stenosis and Fallot's trilogy.[38] In such cases one can also see, as in children of high altitudes, predominant S waves in the three standard limb leads,[39-42] and a QRS loop directed to the right and anteriorly, showing clockwise rotation in the frontal and transverse projections.[37,43,44]

On the other hand, there are some differential characteristics. At high altitudes, the terminal QRS vectors are commonly of greater magnitude, which contributes to the accentuated right ÂQRS deviation, in spite of the fact that only a moderate pulmonary hypertension presumably exists in these children. The qrS pattern in Lead II is more frequent at high altitudes, and the high-voltage QRS complexes in the six limb leads are rather rare. The R wave in the right precordial leads is frequently higher in pulmonary stenosis. At high altitude, qR or rsR′ complexes were found only in the additional chest leads but not in Lead V_1, such as is seen in pulmonary stenosis. The abrupt change between Leads V_1 and V_2 from complexes with a tall R wave to rS complexes, such as is seen in Fallot's tetralogy,[45] was never observed at high altitudes. The upward displacement of the RS-T segment with a positive T wave in Leads I, aVL, V_5, and V_6, as seen in Fallot's trilogy,[45] was not found in our study. Finally, the "congenital" P-wave pattern is not seen at high altitudes.

The Electrical Activity of the Heart at High Altitudes and Its Relation to the Mechanisms of Acclimatization.—Right ventricular preponderance is a common finding in the newborn at sea level and at high altitudes. At this age, the weight and thickness of both ventricles is similar,[46-49] there is a mild pulmonary hypertension,[50,51] and a patent ductus arteriosus is the site of a venoarterial shunt of variable magnitude.[52] The small pulmonary arteries and arterioles maintain their fetal structure, showing a narrow lumen and a thick media.[53-55]

Later on, the positive T wave in the right precordial leads becomes negative. This change is observed at sea level and at high altitudes in a period between a few hours and a few days after birth. During this period of life the expansion of the lungs is complete, the pulmonary vascular resistance decreases considerably, the degree of pulmonary hypertension diminishes,[50] and the venoarterial shunt through the ductus arteriosus disappears,[52] in some cases reversing itself into an arteriovenous shunt.[50]

Some weeks after birth, the electrical activity of the heart shows differences between the two places studied. At sea level, the right ventricular preponderance diminishes rapidly, and by the fourth month of age, ÂQRS is generally oriented to the left. At this time, the pulmonary pressure becomes normal,[51,56] the anatomic closure of the ductus arteriosus occurs,[57] and the left ventricle weighs more and is

thicker than the right.[48,49] The small pulmonary arteries and arterioles show structural changes, characterized by thinning of the media and widening of the lumen, acquiring the adult appearance between the third and sixth months of age.[53-55]

At high altitudes the right ventricular preponderance seen in the newborn infant does not diminish. On the contrary, some weeks after birth the T wave in the right precordial leads becomes again positive, and the marked right ÂQRS deviation remains throughout infancy and childhood. In the child of the high altitudes, right ventricular hypertrophy and persistence of the fetal structure in the small pulmonary arteries and arterioles are frequent findings.[58] These findings permit the assumption that pulmonary hypertension is present in infants and children of the high altitudes. The pulmonary hypertension would explain also the high incidence of patent ductus arteriosus in native residents of the high altitudes.[59,60]

The anatomic and functional changes of the pulmonary circulation at high altitudes are probably the consequence of acclimatization to an environment of anoxic anoxia. At sea level, a rise in the pulmonary pressure and an increase in, or the re-establishment of, a right-to-left shunt through the ductus arteriosus were observed in children breathing low-oxygen mixtures a few hours or a few days after birth.[51,52] It is probable that in high altitudes the chronic anoxia determines a persistent pulmonary hypertension, which in turn would facilitate the maintenance of the fetal structure of the small pulmonary arteries and arterioles. On the other hand, a little after birth the adaptive hematologic mechanisms come into play in the high altitudes. The greater volume and greater viscosity of the blood, circulating in lungs with a narrowed arteriolar bed, are factors capable of maintaining the pulmonary hypertension.[61,62]

Right ventricular hypertension is probably the factor responsible for the delayed evolution of the ventricular activation process with age, for the increased magnitude of the terminal QRS vectors, and for the forward orientation of the T loop, determining in this manner the electrocardiographic and vectorcardiographic characteristics of the healthy children living permanently at high altitudes. These characteristics are not comparable with those of normal children at sea level. Therefore, an environment of high altitude is an important source of electrocardiographic and vectorcardiographic variability in healthy children.

SUMMARY

1. Five hundred and forty normal children were studied. Three hundred and fifty at sea level and 190 in Morococha, 14,900 feet above sea level. The comparative study was made in 5 age groups, ranging from newborn to 14 years of age.

2. In the newborn the electrical activity of the heart showed similar characteristics both at sea level and at high altitudes. Some weeks after birth, the evolution of this phenomenon with age showed definite differences between the two places studied.

3. At high altitudes, an accentuated right ÂQRS deviation persists during infancy and childhood. This finding, as well as the characteristics of the QRS

loop and the scalar data of the QRS complex are the consequence of two factors: (a) a marked delay in the evolutionary pattern of the ventricular activation process, and (b) an increase in the magnitude of the terminal QRS vectors.

4. In high altitudes, after the first weeks or months of life, the T loop shifts to a forward position and the T wave becomes positive in the right precordial leads. These characteristics remain throughout infancy and childhood.

5. Our findings indicate that in healthy children of high altitudes a moderate degree of right ventricular hypertrophy exists. This is probably related to the anatomic and functional changes that take place in the pulmonary circulation as a consequence of the mechanisms of acclimatization.

6. The electrocardiographic and vectorcardiographic characteristics of healthy children living permanently at high altitudes are not comparable with those of normal children at sea level. Therefore, a high-altitude environment is an important source of electrocardiographic and vectorcardiographic variability in healthy children.

The authors are indebted to Dr. Víctor Hernandez and to Mr. Julio Cruz for their valuable help with statistical analysis of the data.

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Tricuspid Insufficiency in Pulmonary Embolism

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A major pulmonary embolism usually demonstrates a characteristic electrocardiographic pattern, which has been thoroughly analyzed by numerous cardiologists.[1-3] Occasionally, however, a large embolus may display no such evidence and be a difficult diagnostic challenge, as is well illustrated by a brief case report.

CASE REPORT

E. C. (B.C.H. No. 1672313), a 50-year-old woman was admitted to the hospital with duodenal obstruction caused by metastasis from a previously treated carcinoma of the cervix. A gastroenterostomy was performed under general endotracheal anesthesia. At the conclusion of this procedure the patient's blood pressure suddenly fell to 80/30 mm. Hg, and the pulse rate rose to 150 per minute. An operative intravenous blood transfusion was started in the left saphenous vein just above the medial malleolus. During this procedure it was noted that the venous blood was pulsating and the venous pressure was over 50 cm. of water. Additional treatment with Levophed and cortisone was unavailing, and the patient died in a shock-like state within 9 hours of the operation.

Several hours prior to death an electrocardiogram had been taken which showed tachycardia with no evidence of myocardial infarction or right ventricular strain.

A postmortem examination was obtained (A59-429) which showed bilateral pulmonary emboli to the major pulmonary arterial trunks. The source of the embolism was the left femoral vein.

The diagnostic dilemma produced by such a situation naturally causes confusion as to therapy and prevents any reasonable chance of survival from this precarious state. Why did the electrocardiogram fail to demonstrate a massive pulmonary embolism? This question has baffled us for many years, until in the course of our study on pulmonary embolism we encountered a phenomenon which may not only explain the absence of electrocardiographic findings in massive embolism but may also give a clue to its correct diagnosis.

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METHODS AND RESULTS

Fifteen mongrel dogs were embolized with a 25 per cent barium solution at a rate of 5 c.c. per minute, and recordings were made of the arterial blood pressure, vena caval pressure, and electrocardiogram, using a Sanborn four-channel recording system. With varying dosages of barium the animals exhibited a typical hemodynamic pattern of a rather sudden fall in arterial pressure, a rise in venous pressure, and either marked S-T-segment changes or tricuspid insufficiency followed by death. Table I shows the representative findings during the terminal phases of embolism. Nine animals demonstrated marked S-T-segment changes and no tricuspid insufficiency, and 4 showed no S-T-segment changes but marked tricuspid insufficiency.

A simultaneous study of arterial blood pressure, right ventricular pressure, vena caval pressure, and electrocardiogram was made on 6 animals. As can be seen in Table II, 3 dogs showed S-T-segment changes with no tricuspid insufficiency, and 3 showed the converse of no S-T-segment changes but tricuspid insufficiency.

Fig. 1 shows the two characteristic patterns: Dog RV 5 demonstrates S-T-segment changes but no tricuspid insufficiency; Dog RV 2 shows tricuspid insufficiency with no evidence of S-T-segment changes. Fig. 2 is interesting in that the marked S-T-segment changes which occurred during the terminal phase of embolism (I) in Dog RV 6 disappeared with the onset of tricuspid insufficiency (II).

TABLE I. ARTERIAL BLOOD PRESSURE AND VENA CAVAL PRESSURE CORRELATED WITH PRESENCE OR ABSENCE OF TRICUSPID INSUFFICIENCY AND S-T-SEGMENT CHANGES IN TERMINAL PHASE OF LETHAL PULMONARY EMBOLI

DOG	ARTERIAL PRESSURE (MM. Hg)	VENA CAVAL PRESSURE (MM. Hg)	TRICUSPID INSUFFICIENCY	S-T CHANGES
T 1	20	28/19	0	+
T 2	36/23	15/7	0	+
T 3	25	38/15	+	0
T 4	18	27/9	+	0
T 5	24/12	6/0	0	+
TV 1	35/20	5	0	+
TV 2	65/30	9	0	+
TV 3	45/15	5	0	+
TA 1	34/20	17/6	+	0
TA 2	64/50	3	0	+
TA 3	60/53	60/32	+	0
TAV 1	32/25	25/9	0	+
TAV 2	28/20	10/4	0	+

TABLE II. ARTERIAL PRESSURE, RIGHT VENTRICULAR PRESSURE, AND VENA CAVAL PRESSURE ASSOCIATED WITH PRESENCE OR ABSENCE OF TRICUSPID INSUFFICIENCY AND S-T-SEGMENT CHANGES IN ELECTROCARDIOGRAM IN TERMINAL PHASE OF PULMONARY EMBOLI

DOG	ARTERIAL PRESSURE (MM. Hg)	RIGHT VENTRICULAR PRESSURE (MM. Hg)	VENA CAVAL PRESSURE (MM. Hg)	TRICUSPID INSUFFICIENCY	S-T CHANGES
RV 1	71/30	42/9	9/7	0	+
RV 2	30/20	29/12	20/9	+	0
RV 3	36/30	32/6	9/5	+	0
RV 4	24/12	24/12	13/4	+	0
RV 5	22/16	26/15	8/6	0	+
RV 6	22/6	27/4	−3	0	+

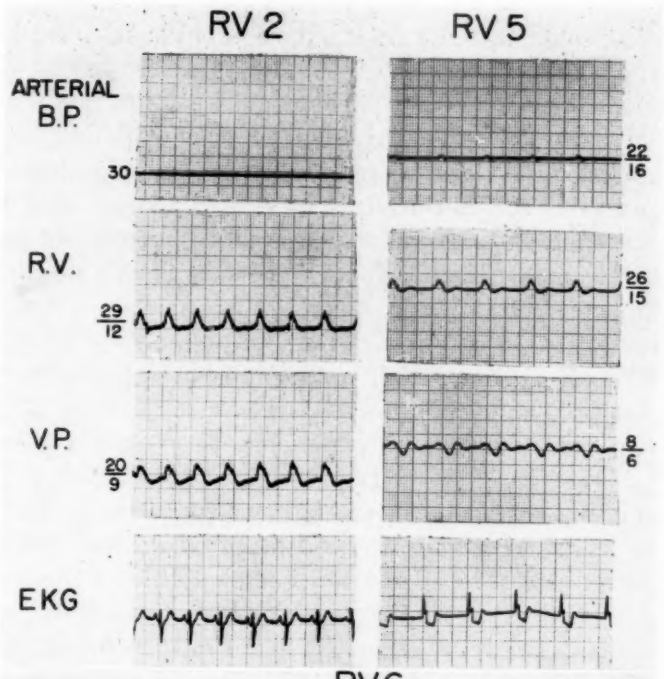

Fig. 1.

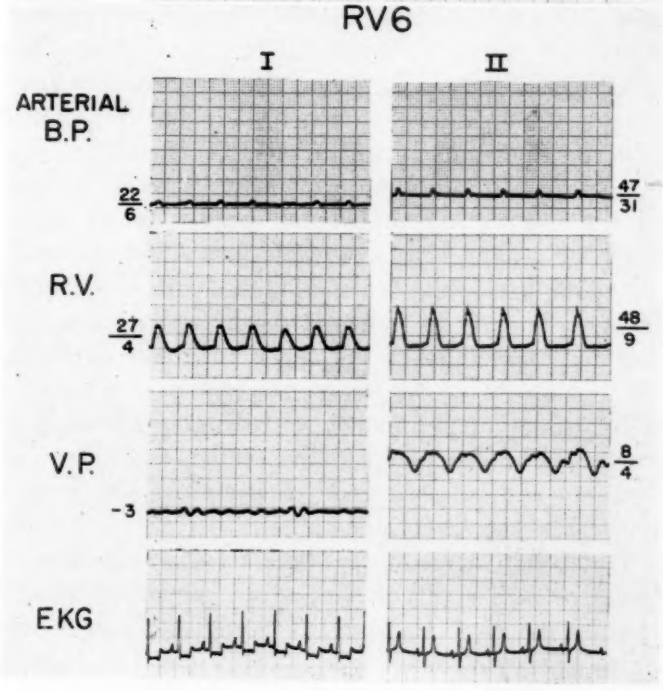

Fig. 2.

Fig. 1.—Typical patterns of hemodynamic and electrocardiographic findings in the terminal phase of lethal pulmonary embolism. Dog RV 2 shows no S-T-segment changes with tricuspid insufficiency, and Dog RV 5 shows no tricuspid insufficiency but marked S-T-segment changes.

Fig. 2.—Hemodynamic and electrocardiographic changes in Dog RV 6, demonstrating (*I*) marked S-T-segment changes with competency of the tricuspid valve, which converted to (*II*) tricuspid insufficiency with disappearance of the S-T-segment changes.

DISCUSSION

This study has demonstrated a constant association between the tricuspid valve function and the electrocardiographic pattern in major experimental pulmonary embolism. If the tricuspid valve remains competent, the usual ECG pattern occurs; but if the tricuspid valve becomes incompetent because of the tremendous dilatation of the right heart, a relatively normal electrocardiogram is recorded. This explains the baffling lack of electrocardiographic evidence for the lethal embolism described in the case report, since this patient had distended veins with a markedly high pulsatile venous pressure, which no doubt was due to tricuspid insufficiency.

Although the electrocardiographic pattern of pulmonary embolism involves changes in the QRS vectors, the QRS-T angle, and S-T-segment vectors, as well as numerous conduction abnormalities, we have stressed the S-T-changes in this report, since in our experimental experience they usually signify a lethal embolism.[4]

We also believe this study sheds some light on the cause of the S-T-segment shift in pulmonary embolism. Since the S-T-segment vectors usually point to the right when plotted according to spatial vector methods, they could be due to left ventricular subendocardial injury secondary to the fall in cardiac output or to right ventricular strain.[5] In reviewing our work, however, there appears to be little correlation between the S-T-segment changes and the systemic blood pressure or the right ventricular pressure. Hence, some other factor must be present. The constant correlation between the electrocardiographic pattern and the tricuspid valve function would seem to indicate that immobility of the dilated and stretched right ventricle is this factor. Coronary blood flow is maximal during ventricular diastole and minimal during systole when the coronary vessels are compressed by the contracting ventricular muscle. If the right ventricle is maximally stretched and attempts to contract against an occluded pulmonary circulation and a competent tricuspid valve, maximal compression of the coronary vessels must take place, leading to ischemia of the right heart. With tricuspid insufficiency, systole and diastole can occur and permit flow in the right coronary artery.

An improved treatment of pulmonary embolism is probably near at hand with the development of the heart-lung pump, which could keep such patients alive until embolectomy can be performed or the clots break up and disperse throughout the lung fields. However, since all embolic patients do not need such heroic treatment, some clinical means of assaying the embolism would be essential. To the usual clinical signs of shock and distended veins with classic electrocardiographic evidence of marked S-T-segment changes we would like to add the finding of tricuspid insufficiency, which can be diagnosed from the venous pressure pattern.[6] When present in the face of a possible pulmonary embolism, it may have the same significance as a positive electrocardiogram.

SUMMARY

Experimental evidence has been presented to show that electrocardiographic changes associated with large pulmonary embolism are caused by an immobile

and tense right ventricle. If tricuspid insufficiency develops from the embolism, the ventricle becomes mobile and the ECG pattern does not occur. Thus, when one suspects a major pulmonary embolism in the absence of a typical electrocardiogram, tricuspid insufficiency should be carefully searched for by studying the venous pressure patterns.

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Case Reports

Cardiac Toxicity of Iproniazid (Marsilid): Report of Myocardial Injury in a Patient Receiving Levarterenol

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Various toxic effects of iproniazid have been recognized. These have been summarized in recent reports.[1-4] Severe myocardial damage has, to our knowledge, not been observed, and the following case is reported because it has important practical and, possibly, theoretical implications.

CASE REPORT

L. M., a 27-year-old white woman, had been under psychiatric care for depressive episodes for a number of years, and her many suicidal attempts with barbiturates had led to numerous hospitalizations. She had always responded to the usual resuscitative measures. Three of these episodes had been followed by acute urinary retention, all of which subsided spontaneously. For 4 to 5 months prior to this admission the patient had been taking dextroamphetamine spansules, 10 mg. daily, chlorpromazine, 50 mg. t.i.d., and two to three 0.1 Gm. secobarbital capsules at night.

In May, 1957, because the depression failed to respond to psychotherapy and the above-mentioned drugs, she was placed on iproniazid by her attending psychiatrist: initially, 50 mg. twice daily, increased in 2 weeks to 50 mg. three times a day. A distinct euphoric effect was noted by the patient and her physician. Three days after the dose had been increased, she began to have syncopal episodes while standing and walking, and fell several times, sustaining numerous bruises. At this time she noted digital paresthesias and, in the upright position, tinnitus, weakness, and vertigo. These symtoms became more severe during the next 10 days, and difficulty in starting micturition was noted. Twelve hours prior to admission, diplopia and nystagmus appeared. She was hospitalized on June 26, 1957, 4 weeks after the initiation of iproniazid therapy.

On physical examination she was found to be a well-developed, thin white woman in discomfort because of acute urinary retention. Multiple ecchymoses were present over the entire body, particularly on the thighs. The blood pressure was 100/60 mm. Hg in the recumbent position, falling to 60/0 mm. Hg when she stood, with an accompanying rise in the pulse rate from 80 to

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142 beats per minute. Standing for a brief period caused peripheral constriction of visual fields, tinnitus, and then syncope. All symptoms disappeared when recumbency was resumed. The urinary bladder was felt 2 inches below the umbilicus. The heart was not enlarged; no murmur or friction rub was heard; heart tones were good, and there was no gallop. Nystagmus was present on lateral gaze in either direction. Deep tendon reflexes were brisk and equal, and there were no pathologic reflexes. The remainder of the physical examination was normal.

Initial routine laboratory studies including a complete blood count, urinalysis, chest x-ray, complete clotting profile, platelet count and bleeding time, and an electrocardiogram were within normal limits. Catheterization yielded 1,290 c.c of urine. She then felt comfortable, as long as she remained recumbent. Symptoms of orthostatic hypotention persisted for 2 weeks after admission.

Initial therapy consisted of bed rest, pyridoxine, 50 mg. t.i.d. orally, and neostigmine by subcutaneous injection at intervals preceding catheterization. Because of her emotional state, dextroamphetamine spansules, 10 mg. every morning, chlorpromazine, 25 mg. t.i.d., and secobarbital, 0.2 Gm. every evening, were continued. Iproniazid had been stopped just prior to admission; however, it was learned later that the patient had brought an indeterminate amount of the drug with her to the hospital and was secretly taking this at her own discretion because of her desperate need for its euphoric effect. On the fifth hospital day, although the symptoms of orthostatic hypotension were unchanged, she was able to urinate normally again. Cystoscopy, on July 3, 1957, showed no abnormality.

On the eighth hospital day, daily intravenous infusions containing levarterenol were begun, the first such containing three 4 c.c. ampules (12 mg.) in 1,000 c.c. of 5 per cent dextrose in water. The rate of this and subsequent infusions was adjusted to maintain her systolic pressure at a level of 140 to 160 mm. Hg, and it took 5 to 8 hours to be completed. At the beginning of the infusion some of the fluid ran freely into the vein while the needle was adjusted and taped in place, and the patient briefly complained of precordial pain at this time. The rate of flow was quickly adjusted to 12 drops per minute. Because of her usual reticence it was not learned until later that this precordial pain persisted for about 90 minute after the speed of infusion had been slowed to this rate. On subsequent days these infusions of levarterenol were repeated, but then consisted of only one 4 c.c. ampule (4 mg.) in 500 c.c. of 5 per cent dextrose in water. While communication with the patient during this period was never really satisfactory for psychiatric reasons, persistent daily inquiries did not elicit any undue complaints. On the fifth day of levarterenol therapy there was some subjective improvement, and the fall in blood pressure when the patient stood was less: from 96/70 to 74/50 mm. Hg. On the sixth day she was fully ambulatory, with only minimal subjective discomfort after the last infusion of levarterenol had been given. On the following day she complained of marked exertional dyspnea on walking to the hall toilet, and then volunteered the information that such dyspnea had been present for 2 or 3 days. A tachycardia, muffled heart tones, but no other abnormalities, were now noted. An electrocardiogram obtained at this time was distinctly different from the one obtained on admission, but with alterations that were considered to be nonspecific (Fig. 1). She was again restricted to her bed, since the slightest activity produced tachycardia and dyspnea. Communication with the patient during this period again was far from ideal, but it could be ascertained that intermittent precordial pain was present, while the signs of iproniazid toxicity had disappeared. Symptoms of orthostatic hypotension no longer were present after the fourteenth day of hospitalization, the blood pressure changing only from 130/84 to 118/80 mm. Hg when she stood.

Serial electrocardiograms showed changes compatible with myocardial injury, as in ischemia of the anterior wall of the heart or myocarditis (Fig. 1), and clinical findings were in keeping with this interpretation. During the third hospital week, microscopic pyuria was found; this was ascribed to the cystoscopy which had been performed during the first week of hospitalization. The condition responded readily to acetyl sulfisoxazole, 1 Gm. q.i.d. for 7 days.

On July 25, 1957, she first noted numbness in the left arm, associated with the intermittent precordial pressure discomfort. A Grade 2, high-pitched apical systolic murmur was heard for the first time. Shortly thereafter she complained of general muscle aching and tenderness. On the next day a biopsy from her left gastrocnemius muscle was normal histologically. Generalized muscular aching and intermittent precordial pain persisted, often lasting for hours, the latter often radiating into the left shoulder. Because an angiitis or myocarditis were considered to be

strong diagnostic possibilities, prednisone, 20 mg. t.i.d., was begun on July 30, 1957. This dosage was gradually decreased over the remainder of her hospital stay. Immediate subjective improvement occurred; the precordial pressure and generalized muscular pains disappeared, and a distinct euphoric effect was noted. Recovery was uneventful from this time on, and she was discharged on Aug. 23, 1957, on 17.5 mg. prednisone daily, after a hospital stay of 2 months.

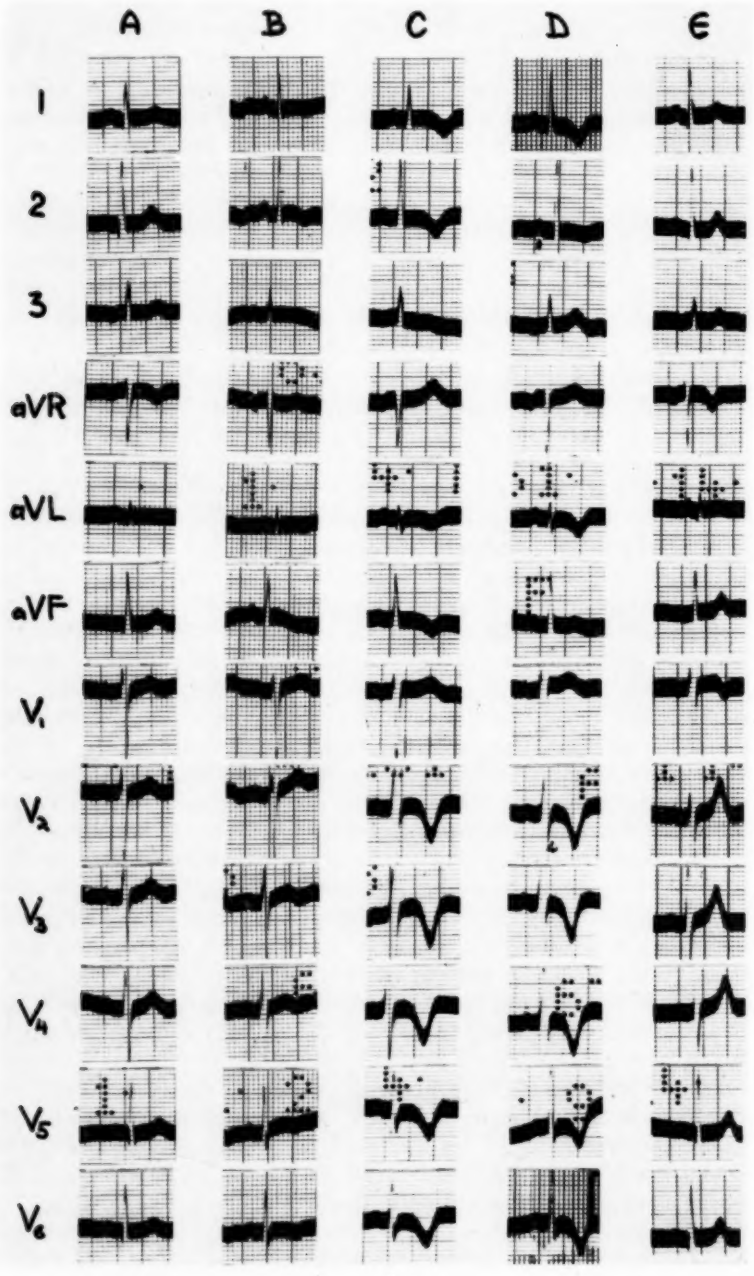

Fig. 1.—Serial electrocardiograms showing a pattern compatible with myocardial injury, with restitution to normal over a period of ten months. *A*, June 27, 1957. *B*, July 8, 1957. *C*, July 18, 1957. *D*, Aug. 14, 1957. *E*, April 11, 1958.

Her subsequent course has been marked by the absence of cardiac symptoms. Restitution of the electrocardiogram to normal was gradual, and a normal tracing was obtained only after 9 months (Fig. 1). Roentgenograms of the chest during this period, and during the acute illness, remained normal; cardiomegaly was never noted.

Prednisone was gradually withdrawn and stopped completely in February, 1958. When she was last seen in May, 1958, all physical findings and laboratory data were within normal limits. However, because of her severe recurring depression and persistent suicidal tendencies, iproniazid had been reinstituted for a period of 10 weeks in dosages of 50 to 100 mg. per day, without any observable ill effect. There was no recurrence of the paresthesias, orthostatic hypotension, cardiac symptoms, or electrocardiographic abnormalities.

DISCUSSION

The problem raised by the events in this case is primarily one of etiology of the myocardial damage. A delayed hypersensitivity reaction with angiitis secondary to iproniazid and similar to that known to complicate the use of sulfonamides seems unlikely because of the patient's subsequent course, and because the readministration of the drug 9 months later was associated with no ill effects. It is true that urticaria due to penicillin, for example, is not necessarily followed by allergic manifestations if this drug is readministered at a later date. Nevertheless, the time relationship between drug administration and the development of cardiac symptoms argues strongly against an allergic mechanism as the basis for the clinical picture. A direct toxic effect on the myocardium, similar to that seen following the administration of emetine, is also unlikely because of the uncomplicated course on prolonged readministration. The cardiac abnormalities, therefore, are ascribable to unusual sensitivity of this individual to levarterenol, with the development of acute myocarditis or to the occurrence of a myocardial infarct which healed. This heightened sensitivity would appear to be the result of prior administration of iproniazid.

It is well known now that iproniazid inhibits amine oxidase, an enzyme which oxidizes various pressor amines, among them levarterenol.[5-8] Levarterenol is liberated at sympathetic nerve endings acting on the smooth muscles of arterioles. It, therefore, is very important in the maintenance of normal blood pressure, especially in the mediation of the pressor responses to postural and other changes. When the destruction of levarterenol is inhibited because the enzyme system responsible for its oxidation is not functioning, larger amounts of the material remain active. Similarly, exogenously administered levarterenol is not readily disposed of under these circumstances. In the peripheral arterioles an exaggeration of the usual vasoconstrictive effect would be anticipated; the effect of levarterenol on the coronary arteries, however, is one of dilation, and it is unlikely that the etiology of the myocardial damage in our patient was due to a reduction in coronary blood flow.

Raab[9,10] has cited evidence to show that both levarterenol and epinephrine are absorbed by the myocardium and cause a wasteful consumption of oxygen by the heart muscle far beyond the requirements of cardiac work. He believes that angina pectoris is the result of catecholamine-induced metabolic hypoxia of the heart muscle, and that under extreme conditions, ischemic necrosis of the myocardial muscle can occur. Injected levarterenol ordinarily does not produce

conspicuous epinephrine-like effects (tachycardia, inverted T waves) on the heart. This may be a result of pressoreceptor reflexes due to hypertension and the ensuing vagal interference. If the vagus is blocked with atropine, the effects of levarterenol are similar to those of epinephrine.

The observations in our patient seem to fit the hypothesis advanced by Raab. The epinephrine-like effect was obtained since no hypertension was induced and the vagal effect was not brought into play. An excess amount of levarterenol most certainly was present, since the amine oxidase system was blocked by iproniazid.

More than the inhibitory effect on amine oxidase must be incriminated in the usual toxic effect of iproniazid, e.g., orthostatic hypotension. Some other phenomena, such as blockage of levarterenol or inhibition of its release, may take place. Iproniazid is known to cause peripheral neuropathy,[2-4] and it is quite possible that it may also cause a visceral neuropathy similar to that occasionally seen in diabetes mellitus. In this patient, diabetes was not present, and there was no evidence of it on follow-up. Another possibility involves a direct toxic effect of iproniazid on the central nervous system, perhaps similar to the orthostatic hypotension accompanying some encephalitides. Finally, one must consider selective damage to vasodilator and vasoconstrictor nerves, the ultimate effect depending on locally determined sensitivity or dosage of iproniazid.

Cardiac toxicity of iproniazid has been reported by Coates,[3] who refers to a 50-year-old man who died suddenly on the tenth day of iproniazid therapy (4 mg./Kg.). The autopsy showed no cardiac abnormalities, and the presumed cause of death was ventricular fibrillation. He also mentions a second patient who experienced convulsive muscular jerking following the administration of racemic epinephrine hydrochloride (Vaponefrin) by inhalation while on iproniazid. Master[11] also states that iproniazid has been suspected of causing myocardial infarction, but ascribes this to the hypotensive effect of the drug. He suggests that it be marketed with vasopressor drugs, such as ephedrine, to maintain normal blood pressure. In the light of our experience it seems that major toxic side effects can be anticipated from such practice.

The choice of therapy with levarterenol in this case was determined by the small amount of knowledge available about the action of iproniazid. It was thought that by increasing the amount of levarterenol by exogenous administration, the toxic and inhibitory—i.e., hypotensive—effect of iproniazid could be overcome. Prednisone was later used to counteract edema, swelling, and inflammation of the myocardium secondary to ischemia, and because of the possibility that a hypersensitivity angiitis existed; this latter possibility was considered strongly at the time. Pyridoxine is thought to be a valuable adjuvant in the prevention and treatment of iproniazid toxicity (peripheral neuropathy), and any visceral neuropathy might have been benefited by its use.

The question can be raised as to what role, if any, the other medications played in this particular case. The time relationship of levarterenol administration to the production of symptoms was clear cut. Other medications, such as secobarbital, dextroamphetamine, and chloral hydrate were continued without interruption during the patient's illness, without noticeable effects, and we

doubt that they were of significance. The hypotensive effects of chlorpromazine may have contributed to her orthostatic hypotension; this, however, does not seem sufficient to explain the electrocardiographic changes and the anginal pain.

The important conclusion that is demonstrated by this case is that severe myocardial damage may result from the administration of pressor amines, particularly levarterenol, in patients with iproniazid toxicity. It appears probable that levarterenol caused ischemic necrosis of myocardial muscle under these circumstances. An awareness of these potent toxic effects of iproniazid raises the question of the safety of this drug in the therapy of angina pectoris as has been recently advocated.[12] Sudden death is an accepted clinical feature of coronary insufficiency, and one may wonder whether iproniazid could be a contributing or causative factor. It seems that careful and prolonged study is needed here, especially if additional medication is used which depends on amine oxidase in its detoxification.

CONCLUSION

A case is reported of a patient with iproniazid toxicity who developed the clinical and electrocardiographic picture of myocarditis after receiving intravenous levarterenol. Possible explanations of this syndrome are discussed. It is recommended that levarterenol and other pressor amines be used either not at all or with extreme caution in patients receiving iproniazid; they should never be used if toxicity to iproniazid is apparent.

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Anomalous Single Coronary Artery Complicating Ventriculotomy in a Child With Cyanotic Congenital Heart Disease

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INTRODUCTION

The purpose of this report is to describe an anomaly in the origin and distribution of the coronary arterial circulation encountered in a 6-year-old child during surgical treatment of an unusual variety of tetralogy of Fallot. Because of the presence of this abnormality a major coronary arterial branch located on the anterior surface of the right ventricular outflow tract was inadvertently cut when a right ventriculotomy incision was made. A description of the clinical and pathologic findings in this patient are presented in order to emphasize the important role which minor variations in the anatomy of the coronary arteries may play during the procedure of open-heart surgery.[1]

In addition to the anatomic variations in coronary arterial circulation, the patient demonstrated several other rare congenital cardiovascular malformations. By the use of angiocardiography and right heart catheterization it was possible to establish in this patient a preoperative diagnosis of tetralogy of Fallot complicated by (1) absence of the left pulmonary arterial branch and (2) coarctation or stenosis of the right pulmonary artery. In addition, absence of the pulmonary valve was found at necropsy.

CASE REPORT

K. K., a white girl, was first studied in the Congenital Cardiac Clinic of the Children's Hospital of Philadelphia at the age of 3 months, having been referred by Dr. Ernest L. Noone.

Birth of the child took place at home, with the mother unattended after a full-term, uneventful pregnancy. The child weighed 8 pounds and 2 ounces at birth. A cardiac murmur was the only abnormality noted in the newborn period. Initial examination in the Cardiac Clinic when she was 3 months old revealed no overt cyanosis; the infant weighed 11 pounds and 12 ounces and appeared alert, active, and healthy. A systolic murmur was audible over the entire precordium; a moderate degree of cardiac enlargement was noted in the roentgenograms, and the electrocardiogram showed right axis deviation.

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Subsequent examinations at 6-month intervals confirmed the presence of a harsh systolic murmur, loudest in the fourth left intercostal space, where a systolic thrill could be readily palpated. A systolic murmur was audible beneath the left scapula; the pulmonic second sound was relatively loud and not reduplicated. Cyanosis was not observed with certainty until the patient was 2 years old, and at that time only with crying. Nine months later cyanosis was present at rest, and a history of squatting was reported.

Cardiac catheterization was carried out in the spring of 1953, when the child was 3 years old. The findings (Table I) included a pressure gradient between the right pulmonary artery and right ventricle and a right-to-left shunt at an undetermined site. The left pulmonary artery and aorta were not entered with the catheter tip. In retrospect, the flat-topped configuration of the right ventricular pressure curves was suggestive of the presence of a ventricular septal defect in connection with the pulmonary stenosis.[2] No left-to-right shunt was demonstrated. During the next 6 months, two venous angiocardiograms were obtained, one in the left anterior oblique and another in the anterior-posterior view (Fig. 1). These demonstrated infundibular pulmonary stenosis, total absence of the left pulmonary arterial branch, and aneurysmal dilatation of the right pulmonary arterial branch, with a constriction in this artery several centimeters above the conventional level of the pulmonary valve. Early filling of the aorta with contrast material, delayed emptying of the right side of the heart, and a small interatrial communication were also demonstrable from these studies.

During the next 3 years the patient exhibited a gradual downhill course. Cyanosis and exercise intolerance became worse. In view of the presence of only a single pulmonary arterial branch, a decision was made to attempt direct surgical repair of this complex malformation with the use of extracorporeal circulation.

TABLE I. CATHETERIZATION FINDINGS

SAMPLE SITE	OXYGEN		PRESSURE (MM. Hg)
	CONTENT (VOL. %)	(% SATURATION)	
Main Pulmonary Artery	12.82	73.7	18/10
High Right Ventricle	12.54	72.2	86/4
Low Right Ventricle	12.67	72.8	86/4
Right Atrium	12.12	70.7	4/2
Superior Vena Cava	12.26	69.8	—
Femoral Artery	15.22	87.5	100/60 (indirect)
Arterial Oxygen Capacity	18.26	102.5	—

In May, 1957, at the age of 6 years, the patient was admitted to the Hospital of the University of Pennsylvania. Physical examination at this time revealed a rather well-developed, 6-year-old white girl with moderate cyanosis and clubbing but no respiratory distress at rest. The pulse rate was 96 per minute and regular; the respiratory rate was 20 per minute. The blood pressure was 100/70 mm. Hg in all extremities. A systolic thrill was palpable in the third and fourth left intercostal spaces. A loud, harsh, systolic murmur was audible over the entire precordium, maximal in the region of the thrill. A systolic murmur was audible posteriorly on both sides of the chest, louder on the right than on the left. A slightly accentuated, single second heart sound was audible in the second left intercostal space. The lungs were clear. The liver and spleen were not enlarged. The femoral pulses were readily palpable.

Laboratory Studies.—A blood count on admission revealed a hemoglobin level of 18 Gm. per cent, with 6.0 million red blood cells. The white blood cell count was 7,000, with a normal differential. Urinalysis was negative. A coagulogram revealed a low prothrombin complex, which was restored to normal with the oral administration of vitamin K. An electrocardiogram

(Fig. 2) demonstrated right axis deviation and right ventricular hypertrophy. The P waves in Lead II were tall and peaked, indicative of the presence of right atrial enlargement. The P-R interval was 0.20 second, being prolonged for the age and rate. Roentgenograms of the chest (Fig. 3) revealed a cardiac silhouette of top-normal size, which was displaced to the left. The left hemithorax appeared smaller than the right, and the right lung appeared hyperaerated. A large pulmonary arterial branch was evident in the right hilar region, but none could be visualized on the left. The peripheral pulmonary vascular markings in the right lung appeared diminished.

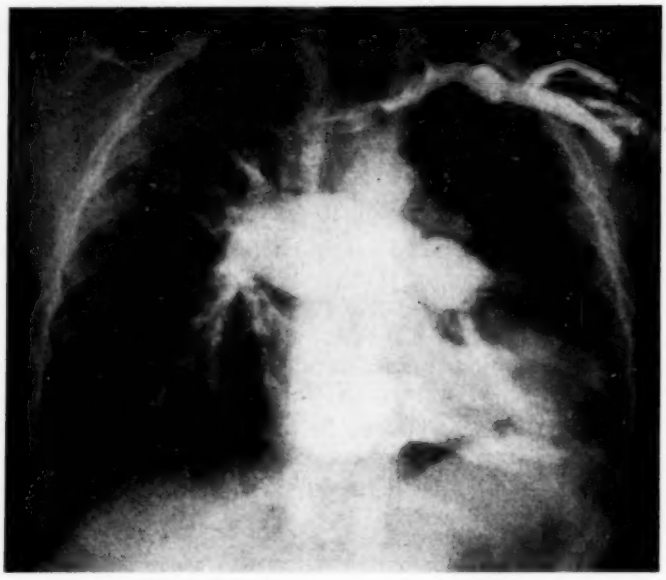

Fig. 1.—Venous angiocardiogram recorded 2 seconds after injection of contrast material. Simultaneous opacification of the pulmonary artery and aorta, infundibular pulmonary stenosis, aneurysmal dilation of the right pulmonary artery, and absence of the left pulmonary artery are demonstrated. (From Stroud and Stroud,[12] p. 133, Fig. 32.)

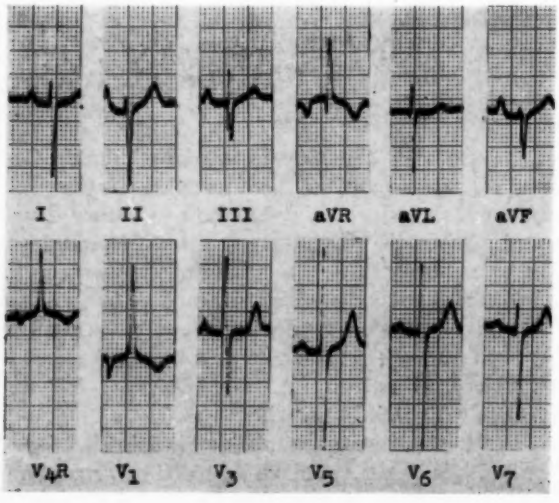

Fig. 2.—Electrocardiogram reveals evidence of right ventricular hypertrophy.

Operation was carried out with the use of a pump-oxygenator. The chest was opened through a transsternal incision in the fourth intercostal space. Examination of the heart revealed a marked thrill in the pulmonary artery, both proximal and distal to the region of coarctation, indicating that two levels of constriction existed, one at the junction of the pulmonary artery and right ventricle and another at the site of the right pulmonary arterial branch constriction. The left pulmonary arterial branch was absent. Catheters were placed in both venae cavae and in the right femoral artery. The right ventricle was opened and a moderate-sized ventricular septal

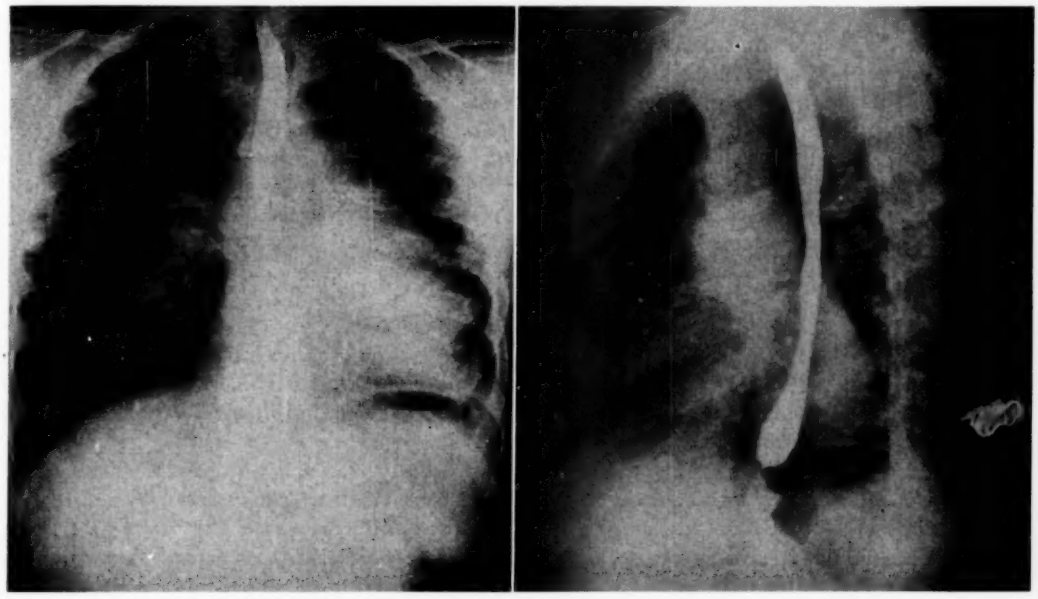

Fig. 3.—Roentgenograms obtained preoperatively. In the anterior-posterior view, displacement of the heart to the left is evident. In the left anterior oblique view the right pulmonary arterial branch is seen end-on as a circular opacification.

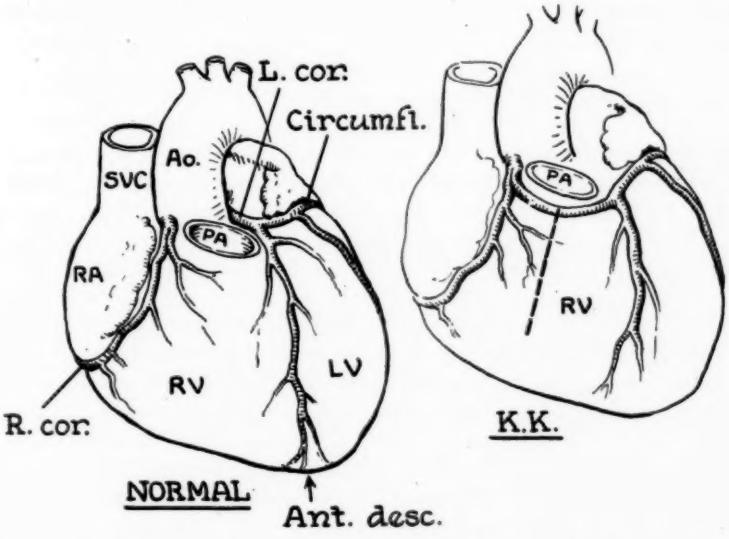

Fig. 4.—Diagram demonstrating distribution of coronary arteries (*left*) in a normal heart and (*right*) in a patient with single right coronary artery. Site of ventriculotomy incision in right ventricular outflow tract is indicated.

defect visualized. The pulmonary stenosis was found to be infundibular in nature and could be relieved by removing pieces of muscle wall in the outflow tract of the right ventricle. An opening sufficient to admit the fifth finger with ease was finally achieved. In order to facilitate relief of the constriction in the right pulmonary arterial branch, the ventriculotomy incision was extended in a cephalad direction. When the incision reached the region of the base of the pulmonary artery, a large coronary arterial branch that was obscured from direct view by a pad of fat tissue was incompletely severed. An effort was made to suture the lacerated vessel with 5-O Deknatel silk. The constriction in the pulmonary arterial branch was then relieved by digital fracture of a diaphragm-like structure situated at the site of the obstruction. The heart was stopped with a 25 per cent solution of potassium citrate for a period of 12 minutes and the ventricular septal defect was closed. Cardiac action was restored and the right ventriculotomy incision closed after 40 minutes on total bypass of the heart and lungs.

The blood pressure was not well maintained, and an intravenous drip of Levophed solution was started. The child was returned to the recovery room, where she awoke from the anesthesia and responded to her name, but shortly thereafter the blood pressure dropped suddenly and could not be restored. The chest was reopened and the right ventricle was seen to be beating, although the left ventricle was not contracting. Cardiac action could not be restored by manual massage.

Autopsy Findings.—The pertinent autopsy findings were those related to the heart, great vessels, and lungs.

The heart weighed 190 grams. The inferior and superior venae cavae entered the right atrium normally; the foramen ovale was patent but was covered by an intact leaflet. The right atrium was dilated. The tricuspid valve ring measured 7 cm. in circumference and appeared normal. The wall of the right ventricle varied from 1.0 to 1.5 cm. in thickness as compared with 0.7 to 0.8 cm. for the left ventricular wall.

There was a high ventricular septal defect, apparently closed by sutures at surgery, but partially reopened during cardiac massage. This defect measured 1.5 cm. in diameter and readily permitted passage of blood from the right ventricle directly into the aorta.

An infundibular stenosis of the outflow tract of the right ventricle was present, but had been relieved to a marked degree by surgery. Two centimeters distal to the infundibular stenosis was a diaphragm-like constricting membrane within the lumen of the right pulmonary artery. This membrane showed evidence of having been fractured and its orifice enlarged. The pulmonary valve ring measured 3.5 cm. in circumference. There were no readily identifiable semilunar leaflets. The endocardial surface in the area between the infundibular stenosis and the constricting membrane was smooth and glistening. The pulmonary artery distal to the constriction was dilated and entered only the right lung; not even a rudimentary left pulmonary arterial branch was seen. The ductus arteriosus was obliterated. The left bronchial artery was easily identified and appeared larger than normal. The pulmonary veins, left atrium, and aortic valve were normal.

Only one coronary artery, corresponding in origin to the right coronary artery (Fig. 4), arose from behind the anterior cusp of the aortic valve. This vessel could be followed in the atrioventricular sulcus for a distance of 1 cm. from the aorta and then gave off a left branch, which extended toward the left for 2 cm. and then divided into normal anterior descending and circumflex branches. The left coronary artery thus passed over the anterior surface of the outflow tract of the right ventricle just below the level of the pulmonary valve.

The suture line in the anterior wall of the right ventricle paralleled the septum and measured 6 cm. in length. The superior extremity of the surgical incision in the right ventricle lacerated the anomalous portion of the left coronary arterial branch. An attempt had been made to suture the torn vessel, but a suture partially occluded the origin of the left anterior descending branch.

Histologic examination of the heart revealed no abnormalities of the myocardium and no evidence of infarction. The constricting membrane in the right pulmonary artery consisted of valvular-type tissue. Proximal to the band, the wall consisted of dense connective tissue. There was no valvular tissue seen in this area nor at the usual site of the pulmonary valve.

Scattered areas of atelectasis were present throughout both lungs. Large bronchial arteries were found to enter the left lung, but it was not possible to differentiate microscopically the smaller bronchial arterial subdivisions from pulmonary arterial branches of the same size. In the left lung there were chronic changes consisting of fibrosis and epithelization of alveoli.

DISCUSSION

In 1952, when the major cardiac malformations in this patient were identified, open-heart surgery was not widely practiced. At that time, her clinical condition was relatively good, and it was decided to defer any attempt at surgical treatment since creation of a subclavian-pulmonary arterial anastomosis was known to be very hazardous in the presence of only one pulmonary artery. By 1957, the patient's clinical state had deteriorated significantly, and operation by the open-heart technique was practicable. With the patient on cardiac bypass, it was planned to relieve the obstruction in both the outflow tract of the right ventricle and the single pulmonary arterial branch and also to close the ventricular septal defect.

The two remaining defects, namely, absence of the left pulmonary artery and absence of the pulmonary valve, would have persisted as potentially handicapping lesions not amenable to surgical correction. Isolated absence of a major pulmonary arterial branch is associated with considerable longevity,[3] although it is occasionally complicated by hemoptysis requiring pneumonectomy.[4] Six instances of congenital absence of the pulmonary valve in association with the tetralogy of Fallot have been described recently by Miller, White and Lev.[5] This anomaly was also observed at necropsy by Campeau, Ruble and Cooksey[6] in a patient dying at the age of 32 years of congestive heart failure which resulted primarily from a large ventricular septal defect associated with pulmonary hypertension. Their patient also had an anomalous single right coronary artery similar in type to the one found in our patient.

In the recent review of Smith,[7] three major anatomic varieties of single coronary artery are listed: (1) a single coronary artery which follows the course of either the normal right or left coronary artery and supplies blood to the entire myocardium by simple extension of its usual subdivisions; (2) a single coronary artery which branches into two major branches shortly after originating from the aorta, each of these branches then following the normal distribution of the normal right and left coronary arteries; and (3) a single coronary artery so abnormal in distribution that it cannot be compared with either the right or left coronary artery. Of the 42 cases of single coronary artery classified by Smith, 10 were of the first type, 17 were of the second type, and 15 were of the atypical type. The anomaly displayed by the patient described in this report belonged to the second category, since the single right coronary artery divided into two branches shortly after emerging from the aorta, and each of these branches then followed the general distribution of the normal right and left coronary arteries. Misplacement of one of the coronary arterial anlages has been offered as an embryologic explanation for this variety of single coronary artery; instances of single coronary artery following the normal distribution on one normal vessel are attributed to a congenital absence of one of the coronary arterial anlages. Absence of the right and left coronary arteries occurred in an approximately equal number of instances.

In Smith's tabulation of patients with single coronary artery, 27 were adults; males were 3 times more frequently affected than females. None of the adults

demonstrated any other congenital cardiovascular malformations. The cause of death was related to cardiac disease in 9 subjects; coronary artery occlusion was found in 4. In addition, there were 13 infants and 1 child in this group with single coronary artery. In 11 of the 14 pediatric subjects the distribution of the single coronary artery was atypical and did not follow the course of either the normal right or left coronary arteries. In contrast to the adult group, 9 of the younger age group demonstrated other congenital anomalies of the cardiovascular system. The average duration of life among the 13 infants was 7 months; one child survived to the age of 5 years.

The single coronary ostium in our patient was located behind the anterior cusp of the aortic valve. One centimeter after emerging from the aorta the single vessel divided into two large, equal subdivisions. One branch was directed posteriorly and took the usual course of the right coronary artery. The anterior branch which followed the distribution of the left coronary artery, upon reaching the region of the interventricular sulcus, yielded normal anterior descending and circumflex branches. There was no microscopic evidence of inadequate myocardial blood supply.

Because of its anomalous site of origin from the single right coronary artery the initial portion of the left coronary branch passed over the anterior surface of the outflow tract of the right ventricle immediately below the usual level of the pulmonary valve. No major coronary arterial branches are normally situated in this position. This region is often obscured by the presence of a pad of fat tissue.

Instances of single *left* coronary artery of the same type as that found in our patient have been described.[8] In these cases a branch which follows the normal course of the right coronary artery comes off the single left coronary artery shortly after the latter arises from the aorta. In coursing from left to right, the branch to the right ventricle may also pass over the anterior surface of the outflow tract of the right ventricle and provide the same surgical hazard at the time of right ventriculotomy. This danger is not present in those instances of single coronary artery in which the distribution of the single coronary artery follows the normal distribution of that artery which is present.

Awareness of the existence of the anomaly under discussion is undoubtedly the most important factor in preventing the catastrophe which occurred in our patient. Inspection and palpation in the region of the outflow tract of the right ventricle for the purpose of detecting anomalous coronary vessels should be carried out carefully prior to ventriculotomy. Dissection in this region may be necessary, if the area is obscured by the presence of a fat pad. Several instances[9-11] of single right coronary artery of the variety demonstrated by our patient have been reported in which the branch to the left ventricle did not pass over the anterior surface of the heart but was buried within the myocardium in this region and became superficial only at the usual site of origin of the anterior descending branch of the left coronary artery. The avoidance of such an anomalous branch at ventriculotomy might be impossible. By determining the presence or absence of the proximal 2 or 3 centimeters of each of the normal coronary arteries, the existence of a single coronary artery may be suspected. If the

presence of a single coronary artery is recognized, a search should then be made for the pathway of anomalous blood supply to the ventricle with an absent main coronary artery.

SUMMARY

1. A 6-year-old white girl with cyanotic congenital heart disease is described, in whom a congenital anomaly in origin and distribution of the coronary arterial blood supply led to a surgical catastrophe. A major branch of a single right coronary artery which was coursing over the anterior surface of the outflow tract of the right ventricle to supply the left ventricular myocardium was cut accidentally when a right ventriculotomy incision was made with the patient on cardiac bypass.

2. Information concerning single coronary artery is reviewed briefly, with reference to its importance as a surgical hazard in patients undergoing open-heart surgery.

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Congenital Absence of the Aortic Arch

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Complete absence of the aortic arch is one of the rarer congenital anomalies. We have found 37 instances recorded in the literature.[1-4,6-14,16,18,20,22,25] Helen Taussig[24] mentions a case reported previously by Hamburger. We propose to present a recent case and briefly discuss the diagnosis and treatment.

The deformity, which can be considered anatomically and physiologically as an extreme example of coarctation of the aorta, consists of an interruption of the aortic arch, usually between the left subclavian artery and the point of entrance of the ductus arteriosus. Less frequently the aorta is interrupted between the left common carotid and the left subclavian arteries, and rarely, between the innominate and left common carotid arteries. In the latter conditions the left subclavian artery or the left common carotid artery originates from the "ductus arteriosus-descending aorta." The right subclavian artery also has a not infrequent anomalous origin.

CASE REPORT

K. R., a white female infant, was born uneventfully at term in hospital. There was no cyanosis at birth. The color was poor but not appreciably different in the upper and lower parts of the body. The infant was lethargic and fed poorly. The heart beats were regular and forceful, and the rate was 180 per minute. A soft systolic apical murmur was audible. Radiologic examination revealed a slightly enlarged heart (Fig. 1). An acute urinary and a purulent ocular infection occurred during the first 2 weeks; both responded promptly to antibiotic therapy. Admission to hospital was advised when the baby was 3 weeks old, because the liver and spleen were palpable and she was thought to be in early heart failure. A gallop rhythm became apparent. There was radiologic evidence of pneumonia, involving the mid zone and base of the right lung, which persisted for 3 days. An electrocardiogram suggested left ventricular hypertrophy with abnormal T wave and S-T segments, consistent with interventricular septal defect. Erythrocytes numbered 5,110,000, and the hemoglobin was 15.4 Gm. She was treated with antibiotics, digoxin, and Mercuhydrin. After 13 days the baby was discharged, her hospital course having been punctuated by bouts of cyanosis. She continued to nurse poorly at home, became emaciated, developed respiratory distress, and died at the age of 2 months.

Autopsy revealed a poorly developed and poorly nourished female infant weighing 2,540 grams. The heart weighed 50 grams. The aortic arch was interrupted distal to the left subclavian artery (Fig. 2,*C*). The left side of the heart was slightly diminished in size. The ascending aorta was narrow and had the same caliber as that of the aortic valve, which was bicuspid and which had a circumference of 2.1 cm. (Fig. 2,*A*). The coronary arteries were normally distributed.

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The right atrium and ventricle were slightly dilated, and the right ventricular wall was hypertrophic. The pulmonic valve measured 3.0 cm. in circumference. The pulmonary artery (Fig. 2,*B*) was of large size, divided into a wide right branch and a narrow left branch. The ductus arteriosus was funnel-shaped, tapered down to a diameter of 0.3 cm., and united the pulmonary artery to the descending aorta. An interventricular septal defect, measuring 1.0 cm. in diameter, was situated high in the membranous portion of the septum. The foramen ovale was closed. The tricuspid and pulmonic valves had a circumference of 4.7 and 3.7 cm., respectively. The only other congenital anomaly was a Meckel's diverticulum. The viscera were congested. The only notable microscopic findings were confined to the lungs; the pulmonary arteries were prominent and their muscular walls were hypertrophic.

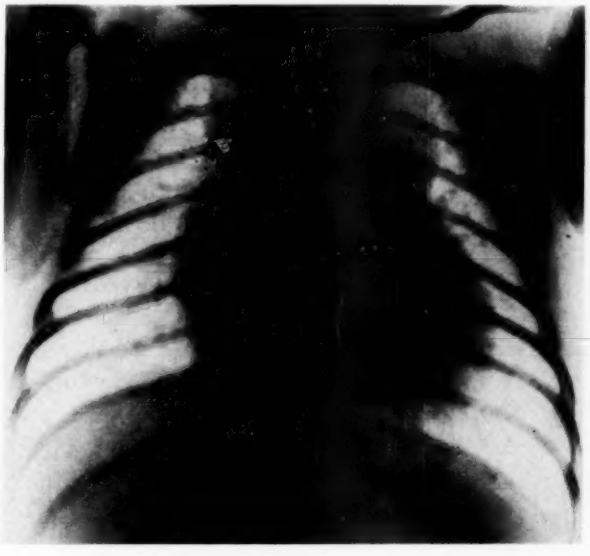

Fig. 1.—Posteroanterior roentgenogram of the chest taken shortly after birth, showing a slightly enlarged heart.

DISCUSSION

Absence of the aortic arch is the result of a minute caudal displacement of the heart and obliteration of the fourth left aortic arch, which in the adult normally develops into that part of the aorta lying between the left subclavian artery and the insertion of the ductus arteriosus. The ductus arteriosus, originally the sixth left aortic arch, persists to supply the descending aorta with blood from the pulmonary artery. The latter is generally prominent. The right ventricle is usually hypertrophic. The ascending aorta tends to be hypoplastic.[13] Hypoplasia of the aorta is often seen also in cases of coarctation and other congenital cardiovascular anomalies.[19] A bicuspid aortic valve or a malformation of the aortic cusps is frequently associated with this anomaly. Lev[15] described these anomalies as "hypoplasia of the aortic tract complexes," whereas Noonan and Nadas[17] also included absence of the aortic arch under the category of "hypoplastic left heart syndrome." Abbott[2] and Hamburger[9] have found congenital absence of the aortic arch in association with transposition of the great vessels. Interruption of the aortic arch is generally associated with interventricular or interatrial septal defects, patent foramen ovale, or patent atrioventricularis communis.

The left-to-right shunt thus produced provides a pathway for the distribution of oxygenated blood, which is supplied to the descending aorta through the patent ductus arteriosus. One of the more frequently encountered noncardiac anomalies is Meckel's diverticulum.

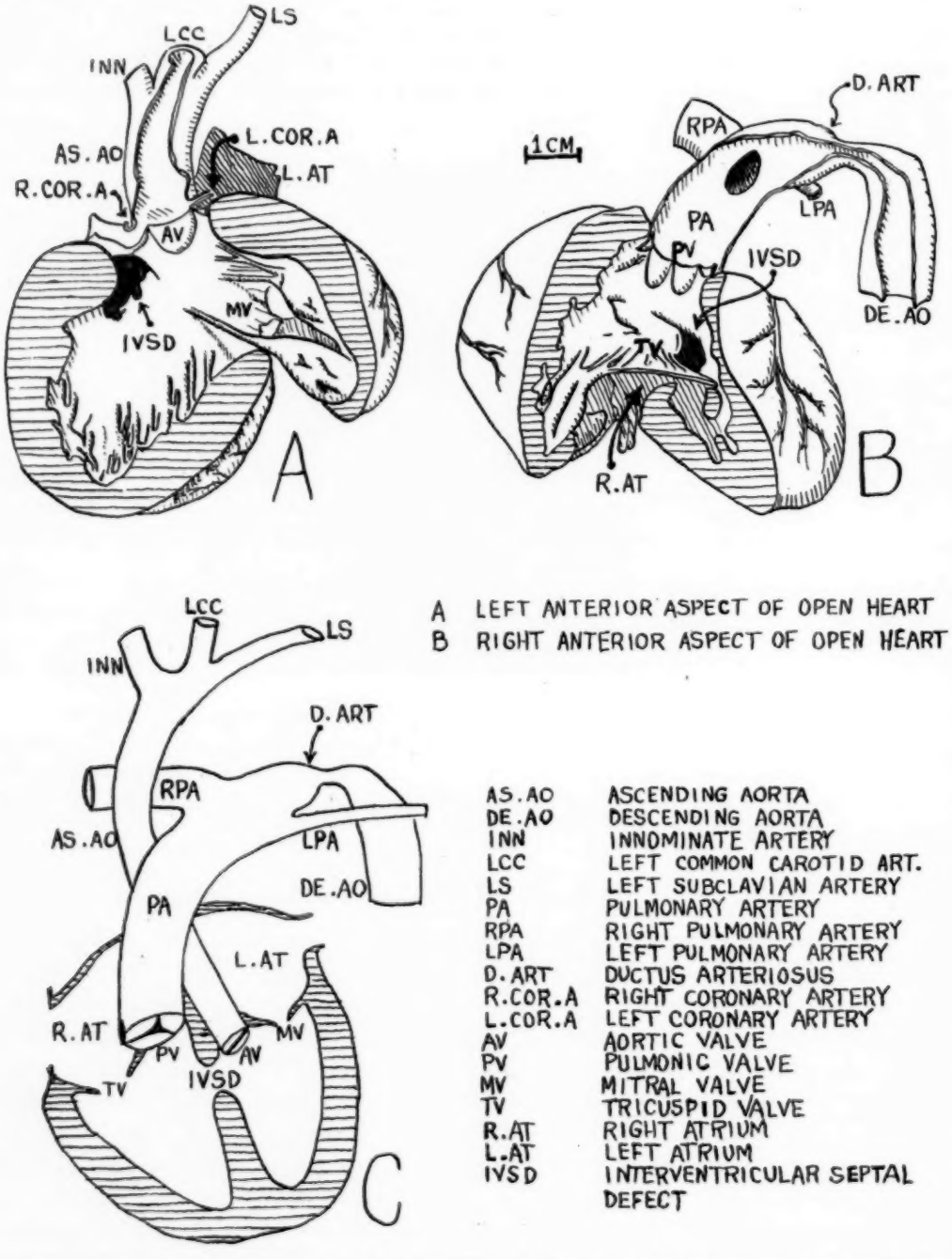

Fig. 2.—Schematic representation of the autopsy findings: complete interruption of aortic arch, hypoplasia of ascending aorta, patent but stenotic ductus arteriosus joining pulmonary artery to descending aorta, interventricular septal defect, bicuspid aortic valve, dilatation of right atrium and ventricle, hypertrophy of wall of right ventricle.

One would expect the trunk and lower extremities to be more cyanotic than the head and upper extremities in this condition. Such "differential cyanosis" has been noted very infrequently[3,6,13,17,20,21] in other reported cases and not at all in ours, despite the narrow passage through which the blood was permitted to enter the descending aorta. Unilateral clubbing of the fingers of the left hand and bilateral clubbing of the toes in a case of absent aortic arch has been reported by Dorney and associates.[6] Absence of differential cyanosis may be explained by the presence of septal defects in the majority of cases, by anomalous origins of arteries arising from the aortic arch, by collateral circulation, by masking due to congestive cardiac failure or respiratory complications, and by the subjective difficulty of assessing minimal color changes clinically.

The physiologic and clinical findings resemble those of severe preductal coarctation with a patent ductus arteriosus and pulmonary hypertension.[5] A significant difference in the blood pressure between the arms and legs could be expected but need not be present in patients with this defect, since the right ventricle compensates for the increased load of supplying most of the systemic circulation by becoming hypertrophic.

The diagnosis of absence of the aortic arch is usually made at autopsy, but cardiac catheterization, angiocardiography, and surgical exploration have permitted Dorney[6] to diagnose the condition in a 6-year-old child. One of Abrams' patients (Case 8) was still alive in 1958, at the age of 4½ years, the diagnosis having been confirmed by angiocardiography and aortography in infancy.[3] Another of his patients (Case 9), who had preductal coarctation with patent ductus arteriosus, underwent a successful surgical correction. The same technique could presumably be applied to the correction of the present lesion. Merrill[16] reported the first case of absent aortic arch which in fact was corrected surgically. Quie and associates[20] have reported a patient (Case 1) in whom surgical intervention was successful, but who died from asphyxia due to a mucous plug on the second postoperative day.

CONCLUSION

Since surgical techniques are now available for correcting absence of the aortic arch, the recognition of this condition becomes of great importance. One of the main clinical observations, within reach of all who are aware of it, is to determine the presence of differential cyanosis between the upper and lower extremities and occasionally of unilateral cyanosis of an upper extremity, simply by placing one limb beside the other and noting variation in color.[23] More elaborate studies such as angiocardiography, aortography, cardiac catheterization, and surgical exploration can then be carried out as required, and definitive treatment applied.

SUMMARY

The case of an infant with complete absence of the aortic arch is discussed briefly in the light of embryological development, clinical investigation, and possibility of surgical correction.

ADDENDUM

Since this report was submitted for publication, 2 instances of differential cyanosis have been reported,[26] in which the skin of the right upper quadrant of the body was pink in color whereas the rest of the body was cyanotic, associated with hypoplasia of the left side of the heart and ascending aorta and premature obliteration of the foramen ovale. We have also found in the recent literature[27,28] 2 more instances of congenital absence of the aortic arch. Apparently, these and our own case bring to 40 the total number of such cases reported in the literature.

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Annotations

Adrenergic Blockade

The medical treatment of severe, progressive, or malignant hypertension is at present based on a series of compounds, structurally similar to acetylcholine, which block cholinergic transmission. The benefits of cholinergic blockade in preserving vision and prolonging useful life are no longer in question; but they have to be paid for by side effects which are troublesome in all patients, and in some are so severe as to limit the effectiveness of treatment, or the patient's tolerance of the regimen. Let us exclude patients with renal failure, who are on that account liable to overdosage from lack of excretion, and also exclude the symptoms associated with postural hypotension, which is clearly inseparable from effective action of the ganglion-blocking agents. We are left with paralysis of accommodation, dryness of the mouth, and constipation, all of which can be attributed to block of the parasympathetic system or of the intrinsic autonomic innervation of the bowel; since this action is no necessary part of the sympathetic inhibition which we are pursuing, we can see why the search has continued for drugs which will block the sympathetic supply to vessels without involving the entire autonomic system. A potent inhibitor of monoamine-oxidase has been shown to lower the blood pressure in primary hypertension[1]; although certain side effects were noted, these were not attributable to parasympathetic blockade. In this annotation, we draw attention to another drug which is effective in lowering blood pressure, but which is also free from the side effects of parasympathetic inhibition.

This drug is a benzyl quaternary ammonium compound, whose chemical name is N-*o*-bromobenzyl-N-ethyl:N:N-dimethylammonium *p*-toluenesulphonate, proprietary name ***Darenthin***, and whose official name in this country is bretylium tosylate, "tosylate" being an approved generic term for salts of p-toluene sulphonic acid. The drug was discovered at the Wellcome Research Laboratories at Beckenham, Kent. The *Lancet* of July, 11, 1959, describes the effects of this drug in animals and in normal and hypertensive men, in a combined paper from the Wellcome Laboratories and the Medical Unit at University College Hospital, London.[2]

Bretylium is not an adrenolytic agent like phentolamine or dibenamine, for the pressor action of injected adrenaline or noradrenaline is enhanced rather than diminished after bretylium has been given. It does, however, effectively block adrenergic transmission, preventing vasoconstriction in the rabbit ear, contraction of the uterus, and relaxation of the duodenum in response to stimulation of the appropriate adrenergic nerve supply. The apparent discrepancy between the lack of adrenolytic action and the effective block of adrenergic transmission may be explained by selective accumulation of the drug in the relevant sites of action. When C^{14}-labelled Darenthin was given to cats in a dose of 6.6 mg./Kg., which blocked sympathetic tone, high levels of radioactivity were found in sympathetic ganglia, postganglionic sympathetic fibers, and organs with a rich adrenergic innervation; moreover, the concentrations reached in those sites were comparable to those needed to block transmission in isolated preparations of adrenergic nerves, with local application of the drug. At doses some thirty times the dose needed to block sympathetic transmission, evidence of general neuromuscular block appeared, with phrenic paralysis and weakened response to sciatic stimulation. There was no evidence in the animal experiments of parasympathetic block, intestinal paresis, or interference with the central nervous system.

The observations in man conform in a general way to the pattern predictable from the properties of the compound as defined in animals. The effect of the new drug on blood pressure resembles that of the ganglion-blockers in that there is not a great fall in the supine blood pressure, but a striking postural hypotension; the effective dosage varies considerably in different patients, and tends to increase as tolerance develops. Long-term control of severe hypertension has been found to be practicable. The side effects reported in the paper under review include some retrosternal oppression, observed only after intravenous injection in one subject; nasal stuffiness, more striking in normotensive subjects; occasional irregularity of the pulse. These were trivial in comparison with the depression, constipation, and signs of parasympathetic inhibition seen with other hypotensive agents, and notably absent in patients treated with bretylium. The initial dose recommended is 112 mg. of base (200 mg. of Darenthin) three times daily; the ultimate effective dose of base in twenty-four subjects ranged from 130 to 840 mg. three times daily.

In summary, we seem to have in bretylium tosylate a hypotensive agent of promise, which acts by adrenergic blockade, and is thus free from the side effects associated with cholinergic blockers.

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Digitalis Intoxication

Digitalis intoxication has classically presented itself as malaise, nausea, vomiting, diarrhea, yellow vision, heart block, and ventricular arrhythmia. That these symptoms still occur and are being overlooked is exemplified by a recent report of Wernicke's syndrome associated with vomiting from longstanding digitalis intoxication.[1] Lately, however, stress has been laid on a different constellation of signs and symptoms, much more difficult to recognize because they mimic the very conditions for which the drug is given.

An increase in the degree of myocardial decompensation is perhaps the most insidious of these, suggesting as it may to the unwary that additional digitalis is needed rather than less.[2] A sinus tachycardia may be caused by overtreatment either as a result of increased failure with lowered stroke volume or independently from a direct action on the sinus node. It has been stated that the combination of paroxysmal atrial tachycardia and first degree A-V block is pathognomonic of digitalis intoxication; while this has been reported in the absence of digitalis,[3] it certainly is strongly suggestive of digitalis overdosage. Atrial fibrillation, atrial flutter, and nodal tachycardia are also caused by digitalis with some degree of frequency.

There is probably an actual increase in the occurrence of digitalis intoxication in recent years. One cause is the use of long-acting glycosides such as digitoxin in doses that eventually will cause overaccumulation in the body. Another is the ever-increasing use of diuretics with a kaliuretic action. The injectable mercurial diuretics cause potassium loss but are only rarely given in sufficient amounts for this to be of clinical importance. The new and effective oral agents such as chlorothiazide and its derivatives frequently lower serum potassium significantly, however, thereby causing a relative excess of digitalis with the resultant picture of intoxication. It should be noted that cardiotoxicity usually appears before or in the absence of gastrointestinal symptoms in such cases.[4] Vomiting, diarrhea, and gastrointestinal drainage procedures may also lower potassium with similar effects.

Potassium remains the treatment of choice for the syndrome of digitalis intoxication, being sufficient in itself where hypokaliemia is the etiology, but coupled with temporary withdrawal of digitalis when this has been administered in overly large amounts. Caution is indicated in

the administration of potassium since severe digitalis intoxication blocks the entry of this ion into cells, death having been produced experimentally by ordinarily well-tolerated amounts of infused potassium.[5]

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The Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

The electrocardiogram is probably the most reliable means currently available to the clinician for the diagnosis of left ventricular hypertrophy (LVH). With the recent advances in cardiac surgery it has become increasingly important to determine preoperatively the presence or absence of anatomic hypertrophy of the left ventricle.

If the electrocardiogram does not show LVH, can it be concluded that significant hypertrophy of the left ventricle is not present? If electrocardiographic LVH is encountered, can it be concluded that there is anatomic LVH? This brief presentation attempts to answer these questions.

The commonly employed electrocardiographic criteria for LVH include high voltage ($R_I + S_{III} > 25$ mm., $RV_{5-6} > 26$ mm., $SV_1 + RV_{5-6} > 35$ mm., $R_{AVL} > 11$ mm. in a horizontal heart; $R_{AVF} > 20$ mm. in a vertical heart), delay in the onset of the intrinsicoid deflection (OID) (0.05-0.07 second) in left precordial leads, S-T segment depression, and T-wave inversion in left precordial leads and in those limb leads whose major QRS deflection is upright, abnormal left axis deviation (LAD) ($-30°$ or $>$).

Several recent electrocardiographic-pathologic correlation studies have evaluated the reliability and specificity of the major groups of criteria in either isolated or dominant LVH.

The range of positivity of the various groups of electrocardiographic criteria in autopsy-proved cases of LVH has varied widely: high voltage, 29 per cent[1] to over 90 per cent[2,3]; delay in OID, 26 per cent[1] to 53 per cent[4]; S-T segment and T-wave changes, 67 per cent[1] to 86 per cent[3]; abnormal LAD, 21 per cent[1] to 50 per cent.[2]

Nevertheless, employing one or more conventional criteria, a positive electrocardiographic diagnosis was made in 85 per cent of 100 cases of isolated LVH demonstrated at autopsy.[1]

The occurrence of false positive diagnoses of LVH has been recently evaluated.[3,5] Any of the classes of electrocardiographic criteria may occur in the absence of anatomic LVH: high voltage, 11 per cent[5] to 15 per cent[3]; delay in OID, 1 per cent[5] to 6 per cent[3]; S-T-T abnormalities, 7 per cent[3] to 9 per cent.[5] Grant[2] has shown that abnormal LAD may occur in the absence of anatomic LVH in over 50 per cent of the cases.

High voltage in the precordial leads has been demonstrated to be the most frequently positive criterion but also the most frequently responsible for a false positive diagnosis.[3,5] In other words, it is the most sensitive but least specific of the current criteria. High voltage in the limb leads is a less sensitive criterion but less prone to produce false positive diagnoses.[5]

Delay in OID, while occurring less frequently than the other main classes of electrocardiographic criteria, is usually quite helpful when present but seldom is the only criterion present.[3,5] Its occasional occurrence as a false positive diagnosis may be due to incomplete left bundle branch block.

The classic S-T segment depression with upward convexity and T-wave inversion of LVH or "strain" adds to the diagnostic accuracy. However, so many factors may contribute to S-T-T changes, such as digitalis, electrolyte imbalance, ischemia, etc., that it is hazardous to diagnose LVH on the basis of S-T-T changes alone.

There are a number of factors which are known to contribute to false positive and false negative diagnoses of LVH. The age of the patient is important. In normal infants, children, and young adults the voltage, especially in the precordial leads, is commonly greater than it is in older adults. Therefore, broader voltage criteria must be employed for the younger age groups. Emaciation and slender body build may result in a false positive diagnosis, whereas obesity may obscure the electrocardiographic diagnosis of LVH. Another possible cause for a false positive diagnosis of LVH can occur with mitral insufficiency and a giant left atrium.[2]

Associated pathologic conditions such as myocardial infarction,[6] congestive heart failure, pericardial effusion, pleural effusion, anasarca, and pulmonary emphysema may all serve to reduce the amplitude of QRS voltage in proved cases of LVH.

Right bundle branch block (RBBB) has been demonstrated to mask the diagnosis of LVH.[7] Left bundle branch block (LBBB) likewise invalidates the conventional criteria for the diagnosis of LVH.[8] Concomitant right ventricular hypertrophy also may obscure the electrocardiographic diagnosis of LVH.[6,9] A recent study[10] which purported to decry the usefulness of current electrocardiographic criteria for LVH included conditions such as RBBB, LBBB, and myocardial infarction which are known to invalidate the accuracy of such criteria.

In summary, when an electrocardiogram demonstrates one or more of the outlined criteria for LVH (and there is an absence of obvious conditions known to produce false positive results), the likelihood of anatomic hypertrophy of the left ventricle being present is of the order of 90 per cent.[3,5] However, the distinction between isolated or dominant LVH cannot be made from the electrocardiogram. A normal electrocardiogram does not exclude the possibility of anatomic LVH, yet the likelihood of significant isolated or dominant LVH being present in such a situation is only about 15 per cent or less.[1,4,10,11] Minimal or borderline LVH is more difficult to detect electrocardiographically than is more marked anatomic LVH. The presence of more than one of the main classes of electrocardiographic criteria adds to the specificity of diagnosis of LVH.

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Book Reviews

NURSING HOME MANAGEMENT. By Ralph C. Williams, B.S., M.D., Margaret Bull Armstrong, R. N., J. Fred Gunter, Edith McCullough, R. N., and Jack Stiller, New York, 1959, F. W. Dodge Corporation, 230 pages, 75 illustrations. Price $8.50.

The authors, representing the disciplines of medicine, public health, nursing, hospital administration, and licensure, have done an excellent organizational job in this comprehensive guide for the operation of nursing homes.

The book is of a size comparable to the average novel, thus making it easy to handle and store. The pages are semi-glazed, with large, easily readable print. The pictures are clear, and the story they tell is obvious even without the precise captions which accompany them.

Starting with the steps necessary to establish and organize a nursing home, the authors proceed to take the reader in a step-by-step process through most of the procedures basic to the operation of a good nursing home. The text suggests types of occupational therapy and art therapy, but does not discuss these topics in detail. Some readers with special knowledge of certain of the technical matters discussed may differ with the authors. To the average operator of a nursing home the reason for these differences will not be apparent.

The background information, set forth in the preface and introduction, gives the reader a concise statement of facts relating to the development of nursing homes and the problems of management of the aged and chronically ill.

Starting with the chapter on Establishment and Organization, and through the chapters on Business Management, Medical and Nursing Care, Recreational Facilities and Group Programs, Food Service Department, Housekeeping and Laundry Service, Building and Grounds, and a Safety Program, the reader is given in precise, but concise, language an understanding of the procedures essential to the basic operation of a nursing home. The Appendix includes the Code of Ethics and Administrative Principles for Nursing Homes adopted by the American Association of Nursing Homes in 1952, an example of a state licensing law, a check list of essential documents pertaining to the operation of a nursing home, a model for nursing home by-laws, suggested personnel policies, and an example of a general maintenance schedule form.

This textbook is really a manual of procedure. It should be on the desk or bookshelf of every nursing-home operator. It can be extremely useful, also, to those considering the establishment or operation of a nursing home, and to those having to do with the licensing or public supervision of nursing homes.

VOLUME PREMIO VITTORIO MALESCI. Firenzi, Italy, 1959, Edzioni Mediche Italiane, 97 pages.

This volume contains three essays which won a special prize and were considered worthy of publication.

The first essay is entitled "The Hypoxia Test and The Exertion Test in Diagnosis of Coronary Diseases," and is by Dr. Candiani and Dr. Fauda. After defining coronary insufficiency and describing the anoxemia and exertion tests, the authors report the data of numerous published studies and discuss the indications, contraindications, and dangers of these tests. The authors have studied 169 cases with both methods and have reached the conclusion that the exertion

test is more sensitive than the other. However, they consider this test to be more dangerous because the revealing electrocardiographic alterations sometimes require strenuous exertion for their appearance, with the possible onset of arrhythmias, prolonged coronary insufficiency, or heart failure. The final conclusion indicates preference for the hypoxia test, which, however, should be performed in a laboratory.

The second essay, entitled "The Humoral Syndrome of Myocardial Infarct," is by Dr. Andreuzzi, Dr. Maggi, Dr. Marchetti, and Dr. Ragaini. It deals with the blood changes of enzymes, urea, cholesterol and sugar, hematocrit, leukocyte and differential counts, proteins, ESR, C-reactive protein and electrolytes, and the urinary excretion of corticosteroids. The personal observations of 20 cases were started on the same day of the attack and continued until the twenty-fifth day. The following phases were recognized: (a) 1st-2nd day: increase of enzymes and blood sugar; (b) 3rd-5th day: increase of lactodehydrogenase; (c) 5th-10th day: increase in α_2-globulins and sedimentation rate; (d) 10th-25th day: increase of β-globulins while the other data gradually return to normal values. The steroid secretion failed to reveal any increase of activity of the adrenal cortex. The *early changes* were interpreted as being due to both a central mechanism (sugar, leukocytes, fever) and the beginning of necrosis (enzymes, glycoproteins, α_2-globulins, C-reactive protein). The *late changes* were due to reaction of the connective tissue, not limited to the site of infarction. Changes of the nonprotein nitrogen were considered to be due to hemodynamic alterations. The modifications of the blood were considered as a reliable guide for the study of the evolution of the infarct.

The third essay, entitled "Quinidine in Atrial Fibrillation," is by Dr. Noseda, Dr. Pace, Dr. Fauda, and Dr. Klein. There is a detailed discussion of those cases which can be benefited by treatment with quinidine. The authors do not advise doses greater than 3 Gm. daily. The possible association of quinidine with digitalis or the antihistaminics is discussed. Benadryl is considered useful in the maintenance of the sinus rhythm, after the use of quinidine. Cases with a large left atrium and long-lasting fibrillation may be benefited by preliminary treatment with anticoagulants. This would reduce the incidence of thromboembolic phenomena. A prolongation of the Q-T interval was found rather frequently during therapy.

This volume, which has a foreword by Prof. Ville, is of definite interest to cardiologists and internists and contains a complete bibliography.

PHYSIOLOGY OF CARDIAC SURGERY: HYPOTHERMIA, EXTRACORPOREAL CIRCULATION, AND EXTRACORPOREAL COOLING. By Frank Gollan, M.D., Assistant Director of Professional Services for Research, Veterans Administration Hospital, Nashville, Tenn., and Research Associate, Department of Surgery, Vanderbilt University Medical School, Nashville, Tenn. Springfield, Ill., 1959, Charles C Thomas, Publisher, 96 pages, 18 figures. Price $4.50.

This book presents essays on certain physiologic observations related to hypothermia and extracorporeal circulation, but its title is misleading, because many aspects of the physiology of cardiac surgery are not included in the book.

It is difficult to understand what audience the author had in mind when writing the book. Experienced workers in the field of extracorporeal circulation are reasonably familiar with most of the physiologic studies presented, and the uninitiated reader would be dismayed by the emphasis on minutiae and the lack of an over-all appraisal of hypothermia and extracorporeal circulation in the treatment of heart disease.

This book is not recommended to readers of the *American Heart Journal.*

THE OPERATION. By Leonard Engel, New York, 1958, McGraw-Hill Book Company, Inc., 277 pages. Price $4.95.

This book is an attempt to acquaint the lay reader with the substance of a heart operation and the important historical developments that made it possible. After one has read it, there is little doubt that the author has succeeded in an admirable fashion. The patient, the operating room, the surgeons, and the operation itself are described so vividly, yet without melodrama,

that one feels he is sitting in the observation dome watching the procedure. Mr. Engel's descriptions, in language any layman can understand, of the workings of a heart-lung machine and its role in open-heart operations is accurate and timely in view of the voluminous amount of material appearing almost daily in the lay press regarding heart surgery.

It is particularly fitting that the book should be about the University of Minnesota and the Department of Surgery in particular. This Department, under the leadership of Dr. Owen Wangensteen, has an enviable record in surgical research and in making significant contributions to surgical progress. Mr. Engel's account of the pioneering work of Dr. Lillehei and Dr. Varco in open-heart surgery serves to emphasize the importance of these contributions.

Because of the accuracy with which the author has described an open-heart operation, this volume should be of interest to technicians working in surgical laboratories, to nurses working on wards and in recovery rooms, and to others who are directly or indirectly concerned with patients having heart disease. For the layman it should prove to be an exciting story.

Announcements

An INTERNATIONAL CONGRESS OF PHLEBOLOGY will be held at Chambery, Savoie, France, on May 6, 7, and 8, 1960.

The Secretaries are: Dr. J. Marmasse, 3, Rue de la République, Orleans, Loiret, and Dr. S Bourgeois, 8, Boulevard du Théâtre, Chambery, Savoie, France.

THE SIXTH BIENNIAL CARDIOVASCULAR SEMINAR will be held at the Balmoral Hotel, Miami Beach, Fla., April 27 to 30, 1960.

For further details, write the Heart Association of Greater Miami, 2 S.E. 13th St., Miami 32 Fla.

Two approved RESIDENCIES IN CARDIOLOGY, to begin July 1, 1960, are being offered at the City of Hope Medical Center, Duarte, Calif. The Residencies will emphasize clinical aspects of diagnosis and treatment of heart disease, and cardiac catheterization, and will provide training in techniques of physiologic investigation of patients with cardiovascular disorders.

Candidates must be graduates of approved medical schools and, except in unusual instances, must have completed at least one year of residency training in Internal Medicine. Residencies are for a period of one year and may be renewed for one additional year, with salary stipend of $4,800.

Facilities are available for housing and maintenance on the grounds, and these facilities can accommodate wives, but not children.

Correspondence should be addressed to B. J. Allenstein, M.D., F.C.C.P., Acting Chief, Department of Cardiology, City of Hope Medical Center, Duarte, Calif.

An INTERNATIONAL SYMPOSIUM will be held in Milan, Italy, on June, 2-4, 1960, for the purpose of reviewing the present status of biological and clinical research on "drugs affecting lipid metabolism."

The agenda will include four main subjects: (1) New data on cholesterol and lipid metabolism (biosynthesis, absorption, site, catabolism, excretion, abnormal pathways). (2) Experimental methods for the evaluation of drugs affecting cholesterol and lipid metabolism (new analytical methods and pharmacological tests). (3) Drugs affecting cholesterol and lipid metabolism in relation to the prevention and treatment of experimental atherosclerosis. (4) Clinical methods and therapeutical significance of drugs affecting cholesterol and lipid metabolism.

The Symposium is sponsored by the Institute of Pharmacology of the University of Milan. and will be under the Chairmanship of Prof. E. Trabucchi. The official languages are Italian and English. Simultaneous translation will be available. The registration fee is U.S. $10. Further announcements will inform about the detailed program.

Until March 1, 1960, information on participation and presentation of papers can be obtained from Prof. S. Garattini, c/o Institute of Pharmacology, Via A. del Sarto 21, Milan, Italy.

A CONTINUATION COURSE IN CARDIOVASCULAR DISEASES for general physicians and specialists will be given on Feb. 8-10, 1960, at the Center for Continuation Study, University of Minnesota, Minneapolis, Minn. Lodging and meals will be available at the Center.